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(54) **Title:** NOVEL M_3 MUSCARINIC ACETYLCHOLINE RECEPTOR ANTAGONISTS

(57) **Abstract:** Muscarinic Acetylcholine receptor antagonists and methods of using them are provided.

Novel M_3 Muscarinic Acetylcholine Receptor Antagonists

FIELD OF THE INVENTION

This invention relates to novel derivatives of biaryl amines, pharmaceutical compositions, processes for their preparation, and use thereof in treating M_3 muscarinic acetylcholine receptor mediated diseases.

BACKGROUND OF THE INVENTION

Acetylcholine released from cholinergic neurons in the peripheral and central nervous systems affects many different biological processes through interaction with two major classes of acetylcholine receptors – the nicotinic and the muscarinic acetylcholine receptors. Muscarinic acetylcholine receptors (mAChRs) belong to the superfamily of G-protein coupled receptors that have seven transmembrane domains. There are five subtypes of mAChRs, termed M1-M5, and each is the product of a distinct gene. Each of these five subtypes displays unique pharmacological properties. Muscarinic acetylcholine receptors are widely distributed in vertebrate organs where they mediate many of the vital functions. Muscarinic receptors can mediate both inhibitory and excitatory actions. For example, in smooth muscle found in the airways, M3 mAChRs mediate contractile responses. For review, please see Caulfield (1993 Pharmac. Ther. 58:319-79).

In the lungs, mAChRs have been localized to smooth muscle in the trachea and bronchi, the submucosal glands, and the parasympathetic ganglia. Muscarinic receptor density is greatest in parasympathetic ganglia and then decreases in density from the submucosal glands to tracheal and then bronchial smooth muscle. Muscarinic receptors are nearly absent from the alveoli. For review of mAChR expression and function in the lungs, please see Fryer and Jacoby (1998 Am J Respir Crit Care Med 158(5, pt 3) S 154-60).

Three subtypes of mAChRs have been identified as important in the lungs, M1, M2 and M3 mAChRs. The M3 mAChRs, located on airway smooth muscle, mediate muscle contraction. Stimulation of M3 mAChRs activates the enzyme phospholipase C via binding of the stimulatory G protein Gq/11 (Gs), leading to liberation of phosphatidyl inositol-4,5-bisphosphate, resulting in phosphorylation of contractile proteins. M3 mAChRs are also found on pulmonary submucosal glands. Stimulation of this population of M3 mAChRs results in mucus secretion.

M2 mAChRs make up approximately 50-80% of the cholinergic receptor population on airway smooth muscles. Although the precise function is still unknown, they inhibit catecholaminergic relaxation of airway smooth muscle via inhibition of cAMP generation. Neuronal M2 mAChRs are located on postganglionic parasympathetic nerves. Under normal physiologic conditions, neuronal M2 mAChRs provide tight control of acetylcholine release from parasympathetic nerves. Inhibitory M2 mAChRs have also been demonstrated on sympathetic nerves in the lungs of some species. These receptors inhibit release of noradrenaline, thus decreasing sympathetic input to the lungs.

M1 mAChRs are found in the pulmonary parasympathetic ganglia where they function to enhance neurotransmission. These receptors have also been localized to the peripheral lung parenchyma, however their function in the parenchyma is unknown.

Muscarinic acetylcholine receptor dysfunction in the lungs has been noted in a variety of different pathophysiological states. In particular, in asthma and chronic obstructive pulmonary disease (COPD), inflammatory conditions lead to loss of inhibitory M2 muscarinic acetylcholine autoreceptor function on parasympathetic nerves supplying the pulmonary smooth muscle, causing increased acetylcholine release following vagal nerve stimulation (Fryer et al. 1999 Life Sci 64 (6-7) 449-55). This mAChR dysfunction results in airway hyperreactivity and hyperresponsiveness mediated by increased stimulation of M3 mAChRs. Thus the identification of potent mAChR antagonists would be useful as therapeutics in these mAChR-mediated disease states.

COPD is an imprecise term that encompasses a variety of progressive health problems including chronic bronchitis, chronic bronchiolitis and emphysema, and it is a major cause of mortality and morbidity in the world. Smoking is the major risk factor for the development of COPD; nearly 50 million people in the U.S. alone smoke cigarettes, and an estimated 3,000 people take up the habit daily. As a result, COPD is expected to rank among the top five as a world-wide health burden by the year 2020. Inhaled anti-cholinergic therapy is currently considered the "gold standard" as first line therapy for COPD (Pauwels et al. 2001 Am. J. Respir. Crit. Care Med. 163:1256-1276).

Despite the large body of evidence supporting the use of anti-cholinergic therapy for the treatment of airway hyperreactive diseases, relatively few anti-cholinergic compounds are available for use in the clinic for pulmonary indications.

More specifically, in United States, Ipratropium Bromide (Atrovent©; and Combivent©, in combination with albuterol) is currently the only inhaled anti-cholinergic marketed for the treatment of airway hyperreactive diseases. While this compound is a potent anti-muscarinic agent, it is short acting, and thus must be administered as many as four times daily in order to provide relief for the COPD patient. In Europe and Asia, the long-acting anti-cholinergic Tiotropium Bromide (Spiriva©) was recently approved, however this product is currently not available in the United States. Thus, there remains a need for novel compounds that are capable of causing blockade at mAChRs which are long acting and can be administered once-daily for the treatment of airway hyperreactive diseases such as asthma and COPD.

Since mAChRs are widely distributed throughout the body, the ability to apply anti-cholinergics locally and/or topically to the respiratory tract is particularly advantageous, as it would allow for lower doses of the drug to be utilized. Furthermore, the ability to design topically active drugs that have long duration of action, and in particular, are retained either at the receptor or by the lung, would allow the avoidance of unwanted side effects that may be seen with systemic anti-cholinergic use.

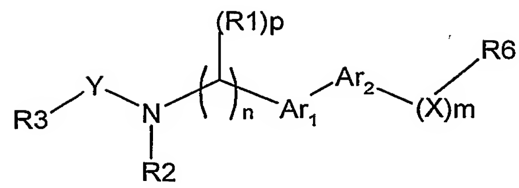
SUMMARY OF THE INVENTION

This invention provides for a method of treating a muscarinic acetylcholine receptor (mAChR) mediated disease, wherein acetylcholine binds to an M_3 mAChR and which method comprises administering an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

This invention also relates to a method of inhibiting the binding of acetylcholine to its receptors in a mammal in need thereof which comprises administering to aforementioned mammal an effective amount of a compound of Formula (I).

The present invention also provides for the novel compounds of Formula (I), and pharmaceutical compositions comprising a compound of Formula (I), and a pharmaceutical carrier or diluent.

Compounds of Formula (I) useful in the present invention are represented by the structure:



(I)

wherein

Ar1 and Ar2, are independently, selected from the group consisting of optionally substituted phenyl and optionally substituted monocyclic heteroaryl;

R6 is NR_7R_8, or an optionally substituted saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more secondary or tertiary nitrogens, and optionally contain one or more O, or S;

X is C(R1)p, or C(O); wherein, when X is C(R1)p, m is an interger from 0 to 3; when X is C(O), m is 1;

p is an interger from 0 to 2;

n is an interger from 0 to 3;

Y is C(O), S(O)q, HNC(O), or OC(O); wherein, q is 1 or 2;

R1 and R2 are independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted heterocylic, optionally substituted heterocyclicalkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aryl alkyl, optionally substituted heteroaryl, and optionally substituted heteroaryl alkyl;

R3 is selected from the group consisting of optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkenyl, optionally substituted C_1-C_{10} alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted aryl alkyl, and optionally substituted heteroaryl alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of halogen, cyano, hydroxy, hydroxy substituted C_{1-10}alkyl, C_{1-10} alkoxy, $S(O)_{m'}$ C_{1-10} alkyl, C(O)R4, $C(O)NR_4R_5$; C(O)OH; $S(O)_2NR_4R_5$, $NHC(O)R_4$, $NHS(O)_2R_4$, C_{1-10} alkyl, alkenyl, halosubstituted C_{1-10} alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroaryl alkyl, wherein these aryl or heteroaryl moieties may be substituted one to

two times by halogen, hydroxy, hydroxy substituted alkyl, C_{1-10} alkoxy, $S(O)_{m'}C_{1-10}$ alkyl, C_{1-10} alkyl, or halosubstituted C_{1-10} alkyl; and m' is 0, 1, or 2;

R_4 and R_5, are independently, selected from the group consisting of hydrogen, optionally substituted C_{1-10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted aryl, optionally substituted aryl alkyl, optionally substituted heteroaryl, and optionally substituted heteroaryl alkyl; or R_4 and R_5 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O, and S;

R_7 and R_8, are independently, selected from the group consisting of hydrogen, optionally substituted C_{1-10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, and optionally substituted heterocyclicalkyl; or R_7 and R_8 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O, N and S;

or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION

The present invention includes all hydrates, solvates, complexes and prodrugs of the compounds of this invention. Prodrugs are any covalently bonded compounds that release the active parent drug according to Formula I **in vivo**. If a chiral center or another form of an isomeric center is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and diastereomers, are intended to be covered herein. Inventive compounds containing a chiral center may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, each tautomeric form is

contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

The meaning of any substituent at any one occurrence in Formula I or any subformula thereof is independent of its meaning, or any other substituent's meaning, at any other occurrence, unless specified otherwise.

Abbreviations and symbols commonly used in the peptide and chemical arts are used herein to describe the compounds of the present invention. In general, the amino acid abbreviations follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature as described in **Eur. J. Biochem.**, 158, 9 (1984).

For use herein the term "the aryl, heteroaryl, and heterocyclic containing moieties" refers to both the ring and the alkyl, or if included, the alkenyl rings, such as aryl, arylalkyl, and aryl alkenyl rings. The term "moieties" and "rings" may be interchangeably used throughout.

As used herein, "optionally substituted" unless specifically defined shall mean such groups as hydrogen; halogen, such as fluorine, chlorine, bromine or iodine; cyano; hydroxy; hydroxy substituted C_{1-10}alkyl; C_{1-10} alkoxy, such as methoxy or ethoxy; $S(O)_{m'}$ C_{1-10} alkyl, wherein m' is 0, 1 or 2, such as methyl thio, methyl sulfinyl or methyl sulfonyl; amino, mono & di-substituted amino, such as in the NR_7R_8 group; $NHC(O)R_7$; $C(O)NR_7R_8$; $C(O)R_7$; $C(O)OH$; $S(O)_2NR_7R_8$; $NHS(O)_2R_7$, C_{1-10} alkyl, such as methyl, ethyl, propyl, isopropyl, or t-butyl; alkenyl, such as ethenyl, 1-propenyl, 2-propenyl, or 2-methyl-1-propenyl; halosubstituted C_{1-10} alkyl, such CF_3; an optionally substituted aryl, such as phenyl, or an optionally substituted arylalkyl, such as benzyl or phenethyl, optionally substituted heterocylic, optionally substituted heterocyclic alkyl, optionally substituted heteroaryl, optionally substituted heteroaryl alkyl, wherein these aryl , heteroaryl, or heterocyclic moieties may be substituted one to two times by halogen; hydroxy; hydroxy substituted alkyl; C_{1-10} alkoxy; $S(O)_{m'}C_{1-10}$ alkyl; amino, mono & di-substituted alkyl amino, such as in the NR_7R_8 group; C_{1-10} alkyl, or halosubstituted C_{1-10} alkyl, such as CF_3.

Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane sulphonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric

acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid and mandelic acid.

The following terms, as used herein, refer to:

- "halo" or "halogen" - chloro, fluoro, bromo and iodo.
- "C_{1-10}alkyl" or "alkyl" - both straight and branched chain moieties of 1 to 10 carbon atoms, unless the chain length is otherwise limited, including, but not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl and the like.
- "C_1-C_{10} alkoxy" includes straight and branched chain radicals of the likes of -O-CH_3, -O-CH_2CH_3, and the n-propoxy, isopropoxy, n-butoxy, sec-butoxy, isobutoxy, *tert*-butoxy, pentoxy, and hexoxy, and the like.
- " C_3-C_{10} cycloalkyl" is used herein to mean cyclic moiety, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, and the like.
- "alkenyl" is used herein at all occurrences to mean straight or branched chain moiety of 2-10 carbon atoms, unless the chain length is limited thereto, including, but not limited to ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.
- "aryl" - phenyl and naphthyl;
- "heteroaryl" (on its own or in any combination, such as "heteroaryloxy", or "heteroaryl alkyl") - a 5-10 membered aromatic ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O or S, such as, but not limited, to pyrrole, pyrazole, furan, thiophene, quinoline, isoquinoline, quinazolinyl, pyridine, pyrimidine, oxazole, tetrazole, thiazole, thiadiazole, triazole, imidazole, or benzimidazole.
- "heterocyclic" (on its own or in any combination, such as "heterocyclicalkyl") - a saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O, or S; such as, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, tetrahydropyran, thiomorpholine, or imidazolidine. Furthermore, sulfur may be optionally oxidized to the sulfone or the sulfoxide.
- "secondary nitrogen" is used herein to mean a nitrogen directly connected to one hydrogen, one optionally substituted carbon, and one optionally substituted carbon, C(O), or S(O)m'; where in m' is 1 or 2.

• "tertiary nitrogen" is used herein to mean a nitrogen directly connected to two independent optionally substituted carbons, and one optionally substituted carbon, C(O), or S(O)m'; where in m' is 1 or 2.

• "quaternary ammonium nitrogen" is used herein to mean a nitrogen directly connected to four independent optionally substituted carbons.

• "arylalkyl" or "heteroarylalkyl" or "heterocyclicalkyl" is used herein to mean C_{1-10} alkyl, as defined above, attached to an aryl, heteroaryl or heterocyclic moiety, as also defined herein, unless otherwise indicated.

• "sulfinyl" - the oxide S (O) of the corresponding sulfide, the term "thio" refers to the sulfide, and the term "sulfonyl" refers to the fully oxidized $S(O)_2$ moiety.

The preferred compounds of Formula I include those compounds wherein:

Ar1 and Ar2, are independently, selected from the group consisting of optionally substituted phenyl and optionally substituted monocyclic heteroaryl;

R6 is an optionally substituted saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more secondary or tertiary nitrogens;

X is C(R1)p, m is an interger from 0 to 3;

p is 2;

n is an interger from 1 to 3;

Y is C(O), or S(O)q; wherein, q is 1 or 2;

R1 is hydrogen

R2 is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted heterocylic, optionally substituted heterocyclicalkyl, optionally substituted aryl, optionally substituted aryl alkyl, optionally substituted heteroaryl, and optionally substituted heteroaryl alkyl;

R3 is selected from the group consisting of optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkenyl, optionally substituted C_1-C_{10} alkyl, optionally substituted C_3-C_{10} cycloalkyl, and optionally substituted C_3-C_{10} cycloalkyl alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of halogen,

cyano, hydroxy, hydroxy substituted C_{1-10}alkyl, C_{1-10} alkoxy, $S(O)_{m'}$ C_{1-10} alkyl, C(O)R4, C(O)NR_4R_5; C(O)OH; $S(O)_2NR_4R_5$, NHC(O)R_4, NHS$(O)_2R_4$, C_{1-10} alkyl, alkenyl, halosubstituted C_{1-10} alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroaryl alkyl, wherein these aryl or heteroaryl moieties may be substituted one to two times by halogen, hydroxy, hydroxy substituted alkyl, C_{1-10} alkoxy, $S(O)_{m'}C_{1-10}$ alkyl, C_{1-10} alkyl, or halosubstituted C_{1-10} alkyl; and m' is 0, 1, or 2;

R_4 and R_5, are independently, selected from the group consisting of hydrogen, optionally substituted C_{1-10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted aryl, optionally substituted aryl alkyl, optionally substituted heteroaryl, and optionally substituted heteroaryl alkyl; or R_4 and R_5 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O, and S;

R_7 and R_8, are independently, selected from the group consisting of hydrogen, optionally substituted C_{1-10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, and optionally substituted heterocyclicalkyl; or R_7 and R_8 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O, N and S;

or a pharmaceutically acceptable salt thereof.

Even more preferred are those compounds where:

Ar1 and Ar2, are independently, selected from the group consisting of optionally substituted phenyl and optionally substituted monocyclic heteroaryl;

R6 is an optionally substituted saturated or partially unsaturated 5-8 membered ring system in which one or more rings contain one or more secondary or tertiary nitrogens;

X is C(R1)p;

R1 is hydrogen

p is 2;

m is 1;

n is 1;

Y is C(O), or S(O)q;wherein, q is 1 or 2;

R2 is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted heterocylic, optionally substituted heterocyclicalkyl, optionally substituted aryl alkyl, and optionally substituted heteroaryl alkyl;

R3 is selected from the group consisting of optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkenyl, optionally substituted C_1-C_{10} alkyl, optionally substituted C_3-C_{10} cycloalkyl, and optionally substituted C_3-C_{10} cycloalkyl alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of halogen, cyano, hydroxy, hydroxy substituted C_{1-10}alkyl, C_{1-10} alkoxy, $S(O)_{m'}$ C_{1-10} alkyl, C(O)R4, C(O)NR_4R_5; C(O)OH; $S(O)_2NR_4R_5$, NHC(O)R_4, NHS$(O)_2R_4$, C_{1-10} alkyl, alkenyl, and halosubstituted C_{1-10} alkyl; wherein m' is 0, 1, or 2;

R_4 and R_5, are independently, selected from the group consisting of hydrogen, optionally substituted C_{1-10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted aryl, optionally substituted aryl alkyl, optionally substituted heteroaryl, and optionally substituted heteroaryl alkyl; or R_4 and R_5 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O, and S;

R_7 and R_8, are independently, selected from the group consisting of hydrogen, optionally substituted C_{1-10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, and optionally substituted heterocyclicalkyl; or R_7 and R_8 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O, N and S;

or a pharmaceutically acceptable salt thereof.

The preferred compounds are selected from the group consisting of:

N-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-3-oxo-2,3-dihydro-1*H*-indene-5-carboxamide bis(trifluoroacetate);

N-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-3-propanoylbenzamide bis(trifluoroacetate);

3-acetyl-*N*-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

N-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-3-(2-oxopropyl)benzamide bis(trifluoroacetate);

3-(ethyloxy)-*N*-({6-fluoro-3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

3-acetyl-*N*-[(3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

3-cyano-*N*-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

3-acetyl-*N*-[(6-(methyloxy)-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

3-cyano-*N*-[(3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

N-({3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-6-fluoro-3-biphenylyl}methyl)-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

3-(ethyloxy)-*N*-({6-(methyloxy)-3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

N-[(3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

3-acetyl-*N*-({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

3-acetyl-*N*-[(3'-{[(3*R*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

N-{[6-fluoro-3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

methyl 3-{[({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)amino]carbonyl}benzoate bis(trifluoroacetate);

3-cyano-*N*-({3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-6-fluoro-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

3-cyano-*N*-({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

3-acetyl-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

3-cyano-*N*-[(6-(methyloxy)-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

3-(ethyloxy)-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

3-cyano-*N*-{[6-fluoro-4'-(methyloxy)-3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

N-({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

N-{[6-fluoro-4'-(methyloxy)-3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

3-(ethyloxy)-*N*-({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

3-acetyl-*N*-({3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

N-({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)-2,1,3-benzoxadiazole-5-carboxamide bis(trifluoroacetate);

N-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-2,1,3-benzoxadiazole-5-carboxamide bis(trifluoroacetate);

N-{[4',6-difluoro-3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

3-(methyloxy)-*N*-({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

3-cyano-*N*-{[4',6-difluoro-3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

3-cyano-*N*-{[6-(methyloxy)-3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

methyl 3-[({[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}amino)carbonyl]benzoate bis(trifluoroacetate);

3-(methylsulfonyl)-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

N-[3-(4-methyl-1-piperazinyl)propyl]-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}octanamide tetrakis(trifluoroacetate);

N-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

methyl 3-{[({3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-3-biphenylyl}methyl)amino]carbonyl}benzoate bis(trifluoroacetate);

3-cyano-*N*-{[3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-6-(methyloxy)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

N-({3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-3-biphenylyl}methyl)-3-(ethyloxy)benzamide bis(trifluoroacetate);

N-{[6-(methyloxy)-3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

N-({3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-3-biphenylyl}methyl)-2,1,3-benzoxadiazole-5-carboxamide bis(trifluoroacetate);

N-({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)-3-(methylsulfonyl)benzamide bis(trifluoroacetate);

3-cyano-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

N-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-3-(trifluoromethyl)benzamide bis(trifluoroacetate);

3-(methyloxy)-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

N-{[3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-6-(methyloxy)-3-biphenylyl]methyl}-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

N-[(3'-{[(3*R*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

3-cyano-*N*-[(3'-{[(3*R*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

N-({3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-3-biphenylyl}methyl)-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

N-({3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-3-biphenylyl}methyl)-3-(methylsulfonyl)benzamide bis(trifluoroacetate);

3-chloro-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

(*E*)-2-phenyl-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}ethenesulfonamide bis(trifluoroacetate);

3-cyano-*N*-({3'-[(1*R*,4*R*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

N-({3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-3-biphenylyl}methyl)-3-(methyloxy)benzamide bis(trifluoroacetate);

N-{[3'-(hexahydro-1*H*-1,4-diazepin-1-ylmethyl)-3-biphenylyl]methyl}-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

4-(methyloxy)-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzenesulfonamide bis(trifluoroacetate);

N-({3'-[(4-acetyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)-1,3-benzodioxole-5-carboxamide trifluoroacetate;

N-({3'-[(2,5-dimethyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

N-({3'-[(3-amino-1-pyrrolidinyl)methyl]-3-biphenylyl}methyl)-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

3-cyano-*N*-({3'-[(2,5-dimethyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

N-({3'-[(3-pyrrolidinylamino)methyl]-3-biphenylyl}methyl)-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

N-({3'-[(4-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

N-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-3-(phenylcarbonyl)benzamide;

3-(ethyloxy)-*N*-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide;

3-acetyl-*N*-[(4-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide;

3-(ethyloxy)-*N*-[(4-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide;

N-[(4-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-3-(phenylcarbonyl)benzamide;

N-[(4-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-1,3-benzodioxole-5-carboxamide;

3-(2-oxo-1-pyrrolidinyl)-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

methyl 2-[({[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}amino)carbonyl]benzoate;

3-[(4-chloro-1*H*-pyrazol-1-yl)methyl]-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

1-methyl-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-1*H*-1,2,3-benzotriazole-6-carboxamide;

3-[(2-hydroxyethyl)oxy]-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

3-[acetyl(methyl)amino]-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

3-[(3,4-dichlorophenyl)carbonyl]-*N*-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide;

3-ethyl-*N*-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide;

N-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide trifluoroacetate;

3-[(2,5-dioxo-4-imidazolidinyl)methyl]-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

methyl {3-[({[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}amino)carbonyl]phenyl}acetate;

3-(3-amino-4,5-dihydro-1*H*-pyrazol-1-yl)-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide trifluoroacetate;

2'-methyl-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-3-biphenylcarboxamide;

3-[(methylamino)sulfonyl]-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

N-methyl-*N'*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-1,3-benzenedicarboxamide;

3-(3,5-dimethyl-4-isoxazolyl)-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

3-[(methylsulfonyl)amino]-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

3-cyano-*N*-[(4-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide;

N-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-2-(3-pyridinyl)-1,3-thiazole-4-carboxamide;

3-acetyl-*N*-{[3-(6-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-2-pyridinyl)phenyl]methyl}benzamide trifluoroacetate;

N-{[3-(6-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-2-pyridinyl)phenyl]methyl}-3-(phenylcarbonyl)benzamide trifluoroacetate;

3-acetyl-*N*-{[3-(5-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-2-thienyl)phenyl]methyl}benzamide trifluoroacetate;

N-{[3-(6-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-2-pyridinyl)phenyl]methyl}-1,3-benzodioxole-5-carboxamide trifluoroacetate;

3-(hydroxymethyl)-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

3-(ethyloxy)-*N*-{[3-(6-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-2-pyridinyl)phenyl]methyl}benzamide trifluoroacetate;

N-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-1,3-benzenedicarboxamide;

N-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-8-quinolinecarboxamide;

3-(aminosulfonyl)-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

3-[(3,4-dichlorophenyl)carbonyl]-*N*-{[3-(6-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-2-pyridinyl)phenyl]methyl}benzamide trifluoroacetate;

N-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-6-(1*H*-pyrrol-1-yl)-3-pyridinecarboxamide; and

3-[(aminocarbonyl)amino]-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

or any other pharmaceutically acceptable salt, or non-salt form thereof.

The most preferred compounds are selected from the group consisting of:

N-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-3-oxo-2,3-dihydro-1*H*-indene-5-carboxamide bis(trifluoroacetate);

N-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-3-propanoylbenzamide bis(trifluoroacetate);

3-acetyl-*N*-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

N-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-3-(2-oxopropyl)benzamide bis(trifluoroacetate);

3-(ethyloxy)-*N*-({6-fluoro-3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

3-acetyl-*N*-[(3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

3-cyano-*N*-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

3-acetyl-*N*-[(6-(methyloxy)-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

3-cyano-*N*-[(3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

N-({3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-6-fluoro-3-biphenylyl}methyl)-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

3-(ethyloxy)-*N*-({6-(methyloxy)-3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

N-[(3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

3-acetyl-*N*-({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

3-acetyl-*N*-[(3'-{[(3*R*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

N-{[6-fluoro-3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

methyl 3-{[({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)amino]carbonyl}benzoate bis(trifluoroacetate);

3-cyano-*N*-({3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-6-fluoro-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

3-cyano-*N*-({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

3-acetyl-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

3-cyano-*N*-[(6-(methyloxy)-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

3-(ethyloxy)-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

3-cyano-*N*-{[6-fluoro-4'-(methyloxy)-3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

N-({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

N-{[6-fluoro-4'-(methyloxy)-3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

3-(ethyloxy)-*N*-({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

3-acetyl-*N*-({3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

N-({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)-2,1,3-benzoxadiazole-5-carboxamide bis(trifluoroacetate);

N-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-2,1,3-benzoxadiazole-5-carboxamide bis(trifluoroacetate);

N-{[4',6-difluoro-3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

3-(methyloxy)-*N*-({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

3-cyano-*N*-{[4',6-difluoro-3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

3-cyano-*N*-{[6-(methyloxy)-3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

methyl 3-[({[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}amino)carbonyl]benzoate bis(trifluoroacetate);

3-(methylsulfonyl)-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

N-[3-(4-methyl-1-piperazinyl)propyl]-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}octanamide tetrakis(trifluoroacetate);

N-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

methyl 3-{[({3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-3-biphenylyl}methyl)amino]carbonyl}benzoate bis(trifluoroacetate);

3-cyano-*N*-{[3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-6-(methyloxy)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

N-({3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-3-biphenylyl}methyl)-3-(ethyloxy)benzamide bis(trifluoroacetate);

N-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-3-(phenylcarbonyl)benzamide;

3-(ethyloxy)-*N*-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide;

3-acetyl-*N*-[(4-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide;

3-(ethyloxy)-*N*-[(4-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide;

N-[(4-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-3-(phenylcarbonyl)benzamide;

N-[(4-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-1,3-benzodioxole-5-carboxamide;

3-(2-oxo-1-pyrrolidinyl)-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

methyl 2-[({[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}amino)carbonyl]benzoate;

3-[(4-chloro-1*H*-pyrazol-1-yl)methyl]-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

1-methyl-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-1*H*-1,2,3-benzotriazole-6-carboxamide;

3-[(2-hydroxyethyl)oxy]-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

3-[acetyl(methyl)amino]-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

3-[(3,4-dichlorophenyl)carbonyl]-*N*-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide;

3-ethyl-*N*-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide;

N-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide trifluoroacetate; and

3-[(2,5-dioxo-4-imidazolidinyl)methyl]-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

or any other pharmaceutically acceptable salt, or non-salt form thereof.

Methods of Preparation

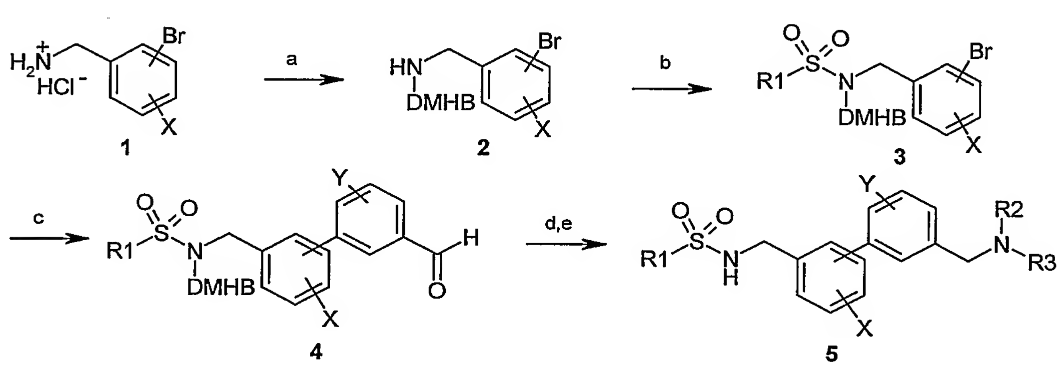
Preparation

The compounds of Formula (I) may be obtained by applying synthetic procedures, some of which are illustrated in the Schemes below. The synthesis provided for these Schemes is applicable for producing compounds of Formula (I) having a variety of different R1, R2, and R3, which are reacted, employing substituents which are suitable protected, to achieve compatibility with the reactions outlined herein. Subsequent deprotection, in those cases, then affords compounds of the nature generally disclosed. While some Schemes are shown with specific compounds, this is merely for illustration purpose only.

Preparation 1

As shown in Scheme 1, bromo benzylamines **1** were loaded onto 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde (DMHB resin) via reductive amination. The resin-bound amines **2** were reacted with various sulfonyl chlorides to yield sulfonamides **3**, which underwent Suzuki coupling with substituted formyl phenyl boronic acids to give biphenylaldehydes **4**. Reductive alkylation of **4** with amines, followed by cleavage with 20% of trifluoroacetic acid in dichoroethane, afforded desired products **5**.

Scheme 1



Conditions: a) DMHB resin, $Na(OAc)_3BH$, diisopropylethylamine, acetic acid, 1-methyl-2-pyrrolidinone, rt; b) $R1SO_2Cl$, pyridine, dichloroethane, rt; c) substituted formyl phenyl-boronic acid, $Pd(PPh_3)_4$, K_2CO_3, dimethoxyethane, 80°C; d) NHR2R3, $Na(OAc)_3BH$, Na_2SO_4, dichloroethane, rt; e) 20% of trifluoroacetic acid in dichoroethane, rt.

SYNTHETIC EXAMPLES

The invention will now be described by reference to the following Examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention. Most reagents and intermediates are commercially available or are prepared according to procedures in the literature. The preparation of intermediates not described in the literature is illustrated below.

Flash column chromatography was carried out using Merck 9385 silica unless stated otherwise.

LC/MS analyses were conducted under the following conditions unless stated otherwise.

- Column: 3.3cm x 4.6mm ID, 3um ABZ+PLUS
- Flow Rate: 3ml/min
- Injection Volume: 5μl
- Temp: Room temperature
- Solvents: A: 0.1% Formic Acid + 10mMolar Ammonium Acetate.
  B: 95% Acetonitrile + 0.05% Formic Acid
- Gradient:

Time	A%	B%
0.00	100	0
0.70	100	0
4.20	0	100
5.30	0	100
5.50	100	0

The Mass Directed Automated Preparative (MDAP) was conducted under the conditions described in System A or in System B unless stated otherwise.

System A: Formate salts

- The preparative column used was a Supelcosil ABZplus (10cm x 2.12cm internal diameter; particle size 5m)
- UV detection wavelength : 200-320nM
- Flow rate : 20ml/min
- Injection Volume: 0.5ml
- Solvent A : 0.1% formic acid
- Solvent B : 95% acetonitrile + 0.05% formic acid

System B TFA salts

- The preparative column used was a Supelcosil ABZplus (10cm x 2.12cm internal diameter; particle size 5m)
- UV detection wavelength : 200-320 nM
- Flow rate : 20 ml/min
- Injection Volume: 0.5 ml
- Solvent A : water + 0.1% trifluoroacetic acid
- Solvent B : acetonitrile + 0.1% trifluoroacetic acid

The Gilson preparatory HPLC was conducted under the following conditions unless stated otherwise.

- Column: 75 x 33mm I. D. , S-5um, 12nm
- Flow rate: 30mL/min
- Injection Volume: 0.800 mL
- Room temperature
- Solvent A: 0.1% trifluoroacetic acid in water
- Solvent B: 0.1% trifluoroacetic acid in acetonitrile

Example 1

Preparation of 4-(methyloxy)-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzenesulfonamide

a) DMHB resin-bound 3-bromo-benzylamine

To a 250 mL shaker vessel was added 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde (DMHB resin) (10 g, 1.5 mmol/g, 15 mmol) and 150 mL of 1-methyl-2-pyrrolidinone (NMP). 3-Bromo-benzylamine HCl salt (17 g, 75 mmol), diisopropylethylamine (DIEA) (13 mL, 75 mmol), acetic acid (HOAc) (15 mL), and $Na(OAc)_3BH$ (19.1 g, 90 mmol) were then added. The resulting mixture was shaken at rt for overnight, and was then washed with NMP (150 mL x 2), dichloromethane (DCM) (150 mL x 2), MeOH (150 mL x 2) and DCM (150 mL x 2). The resulting resin was dried in vacuum oven at 35 °C for overnight to yield DMHB resin-bound 3-bromo-benzylamine (15 mmol).

b) 4-(Methyloxy)-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl} benzenesulfonamide

To a mixture of the above resin-bound 3-bromo-benzylamine (**1a**, 2 g, 1.2 mmol/g (theoretical loading), 2.4 mmol) in 80 mL of dichloroethane (DCE) was added 4-methoxybenzenesulfonyl chloride (5.0 g, 24 mmol) and pyridine (13 mL, 160 mmol). The mixture was shaken at rt for overnight, and was then washed with DCM (100 mL x 2), MeOH (100 mL x 2) and DCM (100 mL x 2). The resulting resin was dried in vacuum oven at 35 °C for overnight. An analytical amount of the resin was cleaved with 20% of trifluoroacetic acid in DCE for 10 min. The resulting solution was concentrated *in vacuo* and dissolved in 0.5 mL of MeOH. MS (ESI): 356 $[M+H]^+$.

To a mixture of the above resin-bound *N*-[(3-bromophenyl)methyl]-4-(methyloxy)benzenesulfonamide (3.38 g, 0.99 mmol/g (theoretical loading), 3.35 mmol) in 83 mL of dimethoxyethane (DME) was added 3-formylphenyl boronic acid (1.49 g, 9.93 mmol), 2 M K_2CO_3 aqueous solution (5 mL, 9.93 mmol) and $Pd(PPh_3)_4$ (0.19 g, 0.17 mmol). After purged with argon for 5-10 min, the mixture was heated at 80 °C for 10 h under argon. The resin was then washed with tetrahydrofuran (THF) (100 mL x 2), THF:H_2O (1:1, 100 mL x 2), H_2O (100 mL x 2), THF:H_2O (1:1, 100 mL x 2), THF (100 mL x 2), DCM (100 mL x 2), and dried in vacuum oven at 35 °C for overnight. An analytical amount of the resin was cleaved with 20% of TFA in

DCE for 10 min. The resulting solution was concentrated *in vacuo* and dissolved in 0.5 mL of CH_3CN. MS (ESI): 382 $[M+H]^+$.

To a mixture of the above resin-bound *N*-[(3'-formyl-3-biphenylyl)methyl]-4-(methyloxy)benzenesulfonamide (400 mg, 0.97 mmol/g (theoretical loading), 0.388 mmol) in 17 mL of DCE was added Na_2SO_4 (0.24 g, 1.68 mmol) and 1,1-dimethylethyl 1-piperazinecarboxylate (0.31 g, 1.68 mmol). After shaking at rt for 10 min, $Na(OAc)_3BH$ (0.43g, 2.02mmol) was added. The mixture was shaken at rt for overnight, and was then washed with THF (100 mL x 2), THF:H_2O (1:1, 100 mL x 2), H_2O (100 mL x 2), THF:H_2O (1:1, 100 mL x 2), THF (100 mL x 2), DCM (100 mL x 2). The resulting resin was dried in vacuum oven at 35 °C for overnight and was cleaved with 6 mL of 20% of TFA in DCE for 30 min and treated again with 6 mL of 20% of TFA in DCE for 30 min. The combined cleavage solution was concentrated *in vacuo*. The residue was dissolved in DMSO and purified using a Gilson semi-preparative HPLC system with a YMC ODS-A (C-18) column 50 mm by 20 mm ID, eluting with 10% B to 90% B in 3.2 min, hold for 1 min where A = H_2O (0.1% trifluoroacetic acid) and B = CH_3CN (0.1% trifluoroacetic acid) pumped at 25 mL/min, to produce 4-(methyloxy)-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzenesulfonamide as a bis-trifluoroacetate salt (white powder, 80 mg, 46% over 5 steps). MS (ESI): 452 $[M+H]^+$.

Proceeding in a similar manner, but replacing 4-methoxybenzene sulfonyl chloride with the appropriate sulfonyl chlorides, and/or replacing 1,1-dimethylethyl 1-piperazinecarboxylate with the appropriate amines, the compounds listed in Tables 1 and 2 were prepared.

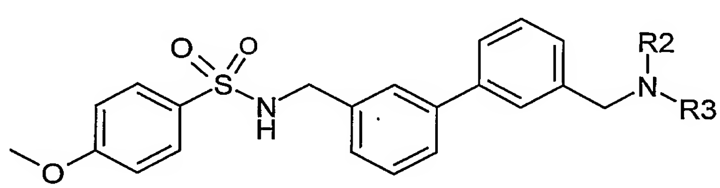


Table 1

Example	NR2R3	MS $[M+H]^+$
2	pyrrolidin-1-yl	437
3	hexahydro-azepin-1-yl	465
4	4-methyl-piperazin-1-yl	466
5	4-methyl-hexahydro-1,4-diazepin-1-yl	480
6	4-ethyl-piperazin-1-yl	480
7	3-amino-pyrrolidin-1-yl	452
8	*N*,*N*-diethyl-amino	439
9	*N*-[2-(dimethylamino)ethyl],*N*-methyl-amino	468
10	hexahydro-1,4-diazepin-1-yl	466
11	(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl	464
12	*N*-piperidin-3-yl-amino	466
13	*N*-pyrrolidin-3-yl-amino	452
14	piperidin-1-yl	451

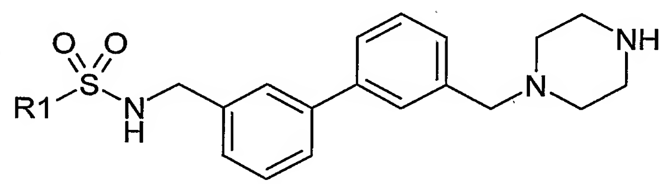


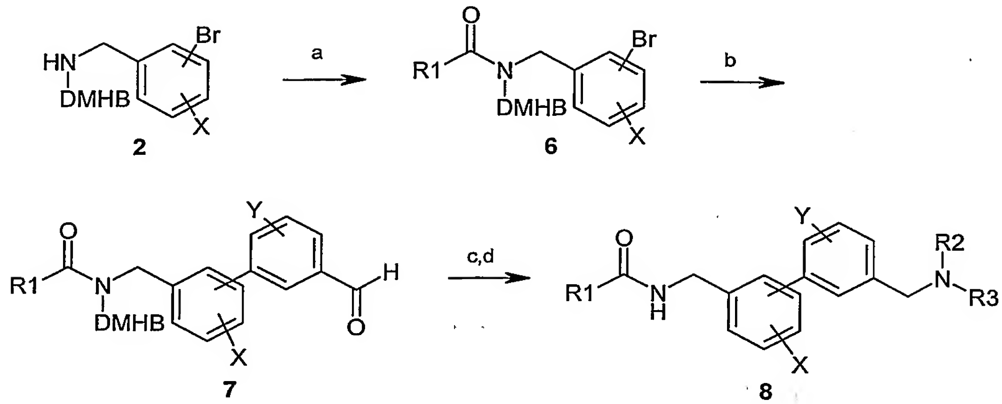
Table 2

Example	R1	MS $[M+H]^+$
15	2,3-dihydro-1,4-benzodioxin-6-yl	480
16	3,4-methylenedioxy-phenyl	466
17	(*1E*)-2-phenyl-ethen-1-yl	448
18	4-(1-methylethyl)-phenyl	464
19	4-n-propyl-phenyl	464
20	3-chloro-phenyl	456
21	2-naphthyl	472
22	5-(*N*,*N*-dimethylamino)-1-naphthyl	515
23	3,4-dimethoxy-phenyl	482
24	3-trifluoromethyl-phenyl	490
25	4-trifluoromethyl-phenyl	490
26	4-(trifluoromethoxy)-phenyl	506
27	4-biphenyl	498
28	8-quinolinyl	473
29	1-naphthyl	472
30	2-fluoro-phenyl	440
31	4-chloro-2,5-dimethyl-phenyl	484
32	2,4,6-trimethyl-phenyl	464
33	2-trifluoromethyl-phenyl	490
34	2,5-dimethoxy-phenyl	482
35	4-fluoro-phenyl	440

Preparation 2

The resin-bound bromobenzylamines **2** were reacted with acids to yield amides **6**, which underwent Suzuki coupling with substituted formyl phenyl boronic acids to give biphenylaldehydes **7** (Scheme 2). Reductive alkylation of **7** with amines, followed by cleavage, afforded desired products **8**.

Scheme 2



Conditions: a) R1CO_2H, 1,3-diisopropylcarbodiimide (DIC), DCM:dimethylforamide (DMF) = 1:1, rt; b) various formyl phenyl-boronic acids, $Pd(PPh_3)_4$, K_2CO_3, DME, 80°C; c) NHR2R3, $Na(OAc)_3BH$, Na_2SO_4, DCM, rt; d) 20% of TFA in DCE, rt

Example 36

Preparation of *N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-1,3-benzodioxole-5-carboxamide

a) DMHB resin-bound *N*-[(3-bromophenyl)methyl]-1,3-benzodioxole-5-carboxamide

To a mixture of DMHB resin-bound 3-bromo-benzylamine (**1a**, 2 g, 1.2 mmol/g (theoretical loading), 2.4 mmol) in DCE/DMF (1:1, 80 mL) was added piperonylic acid (4.0 g, 24 mmol) and DIC (3.7 mL, 24 mmol). The mixture was shaken at rt for overnight and was then washed with DMF (100 mL x 2), DCM (100 mL x 2), MeOH (100 mL x 2) and DCM (100 mL x 2). The resulting resin was dried in vacuum oven at 35 °C for overnight to yield DMHB resin-bound *N*-[(3-bromophenyl)methyl]-1,3-benzodioxole-5-carboxamide (2.4 mmol). An analytical amount of the resin was cleaved with 20% of TFA in DCE for 10 min. The resulting solution was concentrated *in vacuo* and dissolved in 0.5 mL of MeOH. MS (ESI): 334 $[M+H]^+$.

b) *N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-1,3-benzodioxole-5-carboxamide

To a mixture of DMHB resin-bound *N*-[(3-bromophenyl)methyl]-1,3-benzodioxole-5-carboxamide (**36a**, 3.03 g, 1.0 mmol/g (theoretical loading), 3.03 mmol) in 76 mL of DME was added 3-formylphenyl boronic acid (1.36 g, 9.09 mmol), 2 M K_2CO_3 aqeous solution (4.5 mL, 9.09 mmol), and $Pd(PPh_3)_4$ (0.18 g,

0.15 mmol). After purged with argon for 5-10 min, the mixture was heated at 80 °C under argon for 10 h. The resulting resin was washed with THF (100 mL x 2), THF:H_2O (1:1, 100 mL x 2), H_2O (100 mL x 2), THF:H_2O (1:1, 100 mL x 2), THF (100 mL x 2), DCM (100 mL x 2), and dried in vacuum oven at 35 °C for overnight. An analytical amount of the resin was cleaved with 20% of TFA in DCM for 10 min. The resulting solution was concentrated *in vacuo* and dissolved in 0.5 mL of CH_3CN. MS (ESI): 360 $[M+H]^+$.

To a mixture of the above resin (400 mg, 0.99 mmol/g, 0.40 mmol) in 17 mL of DCE was added Na_2SO_4 (0.24 g, 1.7 mmol) and 1,1-dimethylethyl 1-piperazinecarboxylate (0.32 g, 1.7 mmol). After shaking for 10min, $Na(OAc)_3BH$ (0.43 g, 2.04 mmol) was added. After shaken at rt for overnight, the resin was washed with THF (100 mL x 2), THF:H_2O (1:1, 100 mL x 2), H_2O (100 mL x 2), THF:H_2O (1:1, 100 mL x 2), THF (100 mL x 2), DCM (100 mL x 2) and dried in vacuum oven at 35 °C for overnight. The resulting resin was cleaved with 8 mL of 20% of TFA in DCE for 30 min and treated again with 8 mL of 20% of TFA in DCE for 30 min. The combined cleavage solution was concentrated *in vacuo*. The residue was dissolved in DMSO and purified using a Gilson semi-preparative HPLC system with a YMC ODS-A (C-18) column 50 mm by 20 mm ID, eluting with 10% B to 90% B in 3.2 min, hold for 1 min where A = H_2O (0.1% trifluoroacetic acid) and B = CH_3CN (0.1% trifluoroacetic acid) pumped at 25 mL/min, to produce *N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-1,3-benzodioxole-5-carboxamide as a bis-trifluoroacetate salt (white powder, 100 mg, 58% over 5 steps). MS (ESI): 430 $[M+H]^+$.

Proceeding in a similar manner, but replacing piperonylic acid with the appropriate acids, and/or replacing 1,1-dimethylethyl 1-piperazinecarboxylate with the appropriate amines, and/or replacing 3-bromo-benzylamine with appropriate bromobenzylamines, and/or replacing 3-formylphenyl-boronic acid with appropriate formylphenyl boronic acids, the compounds listed in Tables 3 - 13 were prepared.

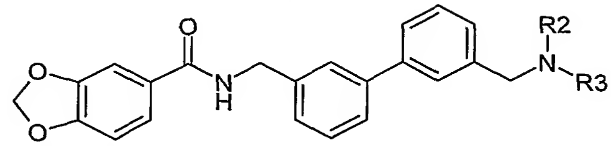


Table 3

Example	NR2R3	MS $[M+H]^+$
37	pyrrolidin-1-yl	415
38	hexahydro-azepin-1-yl	443
39	4-methyl-piperazin-1-yl	444
40	4-methyl-hexahydro-1,4-diazepin-1-yl	458
41	4-acetyl-piperazin-1-yl	472
42	4-ethyl-piperazin-1-yl	458
43	3-amino-pyrrolidin-1-yl	430
44	*N,N*-diethy-lamino	417
45	4-methyl-piperidin-1-yl	443
46	hexahydro-1,4-diazepin-1-yl	444
47	3-amino-piperidin-1-yl	444
48	(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl	442
49	*N*-methyl,*N*-butyl-amino-	431
50	*N*-piperidin-3-yl-amino	444
51	*N*-piperidin-4-yl-amino	444
52	*N*-(hexahydro-azepin-4-yl)-amino	458
53	*N*-pyrrolidin-3-yl-amino	430
54	*N*-[3-(dimethylamino)propyl],*N*-methyl-amino	460
55	piperidin-1-yl	429
56	4-formylpiperazin-1-yl	458

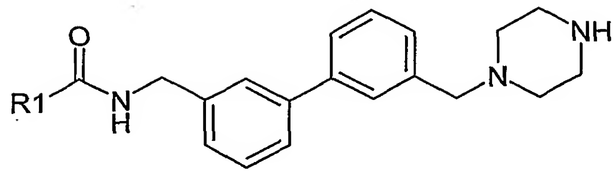


Table 4

Example	R1	MS[M+H]$^+$
57	3,4-dimethoxy-phenyl	446
58	3,4-dichloro-phenyl	454
59	2-naphthyl	436
60	2-quinolinyl	437
61	3-quinolinyl	437
62	4-quinolinyl	437
63	4-pyridinyl	387
64	3-pyridinyl	387
65	2-pyridinyl	387
66	benzofuran-2-yl	426
67	benzothiophen-2-yl	442
68	1H-indol-2-yl	425
69	1H-indol-3-yl	425
70	2-furanyl	376
71	thiophen-3-yl	392
72	3-furanyl	376
73	2-methoxy-phenyl	416
74	2-cyano-phenyl	411
75	2-trifluoromethyl-phenyl	454
76	2-chloro-phenyl	420
77	3-methoxy-phenyl	416
78	3-cyano-phenyl	411
79	3-trifluoromethyl-phenyl	454
80	3-chloro-phenyl	420
81	4-methoxy-phenyl	416
82	4-cyano-phenyl	411
83	4-trifluoromethyl-phenyl	454

84	4-chloro-phenyl	420
85	cyclopropyl	350
86	cyclohexyl	392
87	1-naphthyl	436
88	2,3-methylenedioxy-phenyl	430
89	4-biphenyl	462
90	4-(1,1-dimethylethyl)-phenyl	442
91	4-(but-1-yl)-phenyl	442
92	1-propyl	352
93	1-butyl	366
94	1-pentyl	380
95	1-hexyl	394
96	1-heptyl	408
97	thiophen-2-yl	392
98	3-acetyl-phenyl	428
99	3-ethoxy-phenyl	430
100	3-(methoxycarbonyl)-phenyl	444
101	3-methylsulfonyl-phenyl	464
102	2,2-difluoro-benzo[1,3]dioxol-5-yl	466
103	benzothiazol-6-yl	443
104	3,4-dihydro-2 *H*-benzo[*b*][1,4]dioxepin-7-yl	458
105	benzo[1,2,5]oxadiazol-5-yl	428
106	2,3-dihydro-benzo[1,4]dioxin-6-yl	444
107	2,3-dihydro-benzofuran-5-yl	428
108	3-(phenylcarbonyl)-phenyl	490
109	3-methyl-phenyl	400
110	3-acetylamino-phenyl	443
111	4-hydroxy-3-methoxy-phenyl	432
112	3-ethyl-phenyl	414
113	3-trifluoromethoxy-phenyl	470
114	3-fluoro-phenyl	404
115	3-(toluene-4-sulfonylamino)-phenyl	555
116	3-hydroxy-phenyl	402
117	3-phenoxy-phenyl	478

118	3 *H*-benzoimidazol-5-yl	426
119	4-methoxy-3-hydroxy-phenyl	432
120	phenyl	386
121	phenoxymethyl	416
122	2-methyl-propen-1-yl	364
123	2-phenyl-ethen-1-yl	412
124	4-nitro-phenyl	431

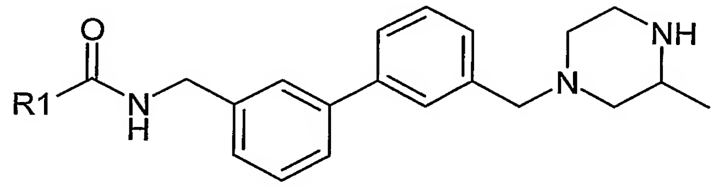


Table 5

Example	R1	MS [M+H]+
125	3-acetyl-phenyl	442
126	3-ethoxy-phenyl	444
127	3-(methoxycarbonyl)-phenyl	458
128	3-methylesulfonyl-phenyl	478
129	2,2-difluoro-benzo[1,3]dioxol-5-yl	480
130	benzothiazol-6-yl	457
131	3,4-dihydro-2 *H*-benzo[*b*][1,4]dioxepin-7-yl	472
132	benzo[1,2,5]oxadiazol-5-yl	442
133	2,3-dihydro-benzo[1,4]dioxin-6-yl	458
134	2,3-dihydro-benzofuran-5-yl	442
135	3-(phenylcarbonyl)-phenyl	504
136	3-methyl-phenyl	414
137	3-acetylamino-phenyl	457
138	4-hydroxy-3-methoxy-phenyl	446
139	3-ethyl-phenyl	428
140	3-trifluoromethoxy-phenyl	484
141	3-fluoro-phenyl	418
142	3-(toluene-4-sulfonylamino)-phenyl	569
143	3-hydroxy-phenyl	416
144	3-phenoxy-phenyl	492
145	3 *H*-benzoimidazol-5-yl	440
146	4-methoxy-3-hydroxy-phenyl	446

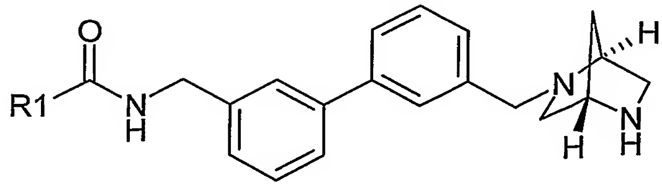


Table 6

Example	R1	MS $[M+H]^+$
147	3-acetyl-phenyl	440
148	3-ethoxy-phenyl	442
149	3-(methoxycarbony)-phenyl	456
150	3-methylsulfonyl-phenyl	476
151	2,2-difluoro-benzo[1,3]dioxol-5-yl	478
152	benzothiazol-6-yl	455
153	3,4-dihydro-2 *H*-benzo[*b*][1,4]dioxepin-7-yl	470
154	benzo[1,2,5]oxadiazol-5-yl	440
155	2,3-dihydro-benzo[1,4]dioxin-6-yl	456
156	2,3-dihydro-benzofuran-5-yl	440
157	3-(phenylcarbonyl)-phenyl	502
158	3-methyl-phenyl	412
159	3-acetylamino-phenyl	455
160	4-hydroxy-3-methoxy-phenyl	444
161	3-ethyl-phenyl	426
162	3-trifluoromethoxy-phenyl	482
163	3-fluoro-phenyl	416
164	3-(toluene-4-sulfonylamino)-phenyl	567
165	3-hydroxy-phenyl	414
166	3-phenoxy-phenyl	490
167	3 *H*-benzoimidazol-5-yl	438
168	4-methoxy-3-hydroxy-phenyl	444

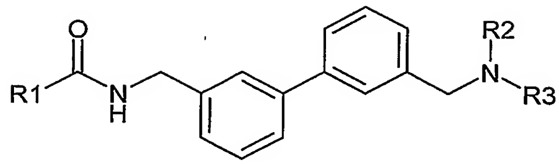


Table 7

Example	R1	NR2R3	MS [M+H]+
169	3-cyano-phenyl	(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl	423
170	3-methoxy-phenyl	(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-yl	428
171	3,4-methylenedioxy-phenyl	1-azabicyclo[2.2.2]oct-3-yl	470
172	3-cyano-phenyl	1-azabicyclo[2.2.2]oct-3-yl	451
173	3-cyano-phenyl	hexahydro-1,4-diazepin-1-yl	425
174	3-methoxy-phenyl	hexahydro-1,4-diazepin-1-yl	430
175	3,4-methylenedioxy-phenyl	2,5-dimethyl-piperazin-1-yl	458
176	3-cyano-phenyl	2,5-dimethyl-piperazin-1-yl	439
177	3-methoxy-phenyl	2,5-dimethyl-piperazin-1-yl	444
178	3,4-methylenedioxy-phenyl	3-methyl-piperazin-1-yl	444
179	3-cyano-phenyl	3-methyl-piperazin-1-yl	425
180	3-methoxy-phenyl	3-methyl-piperazin-1-yl	430
181	3,4-methylenedioxy-phenyl	3,5-dimethyl-piperazin-1-yl	458
182	3-cyano-phenyl	3,5-dimethyl-piperazin-1-yl	439
183	3-methoxy-phenyl	3,5-dimethyl-piperazin-1-yl	444

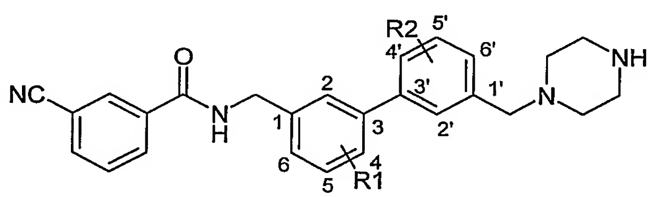


Table 8

Example	R1	R2	MS [M+H]+
184	hydrogen	4'-methoxy	441
185	hydrogen	6'-fluoro	429
186	hydrogen	6'-methoxy	441

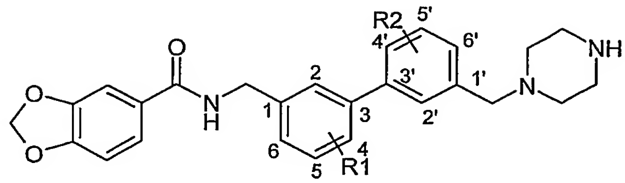


Table 9

Example	R1	R2	MS $[M+H]^+$
187	hydrogen	4'-methoxy	460
188	hydrogen	6'-fluoro	448
189	hydrogen	6'-methoxy	460

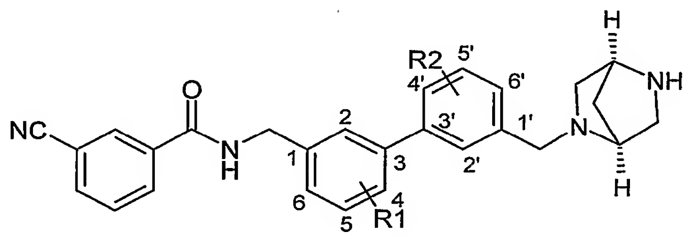


Table 10

Example	R1	R2	MS $[M+H]^+$
190	hydrogen	4'-methoxy	453
191	hydrogen	6'-fluoro	441
192	hydrogen	6'-methoxy	453

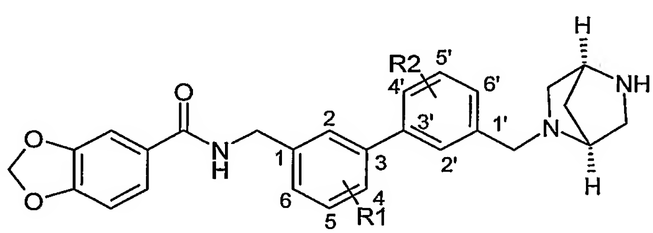


Table 11

Example	R1	R2	MS $[M+H]^+$
193	hydrogen	4'-methoxy	472
194	hydrogen	6'-fluoro	460
195	hydrogen	6'-methoxy	472

Table 12

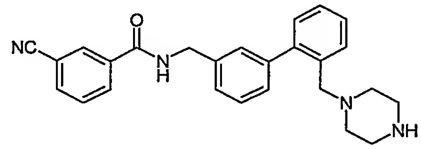
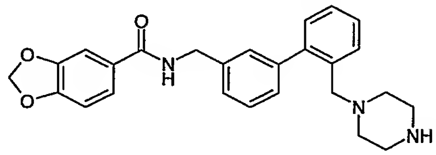
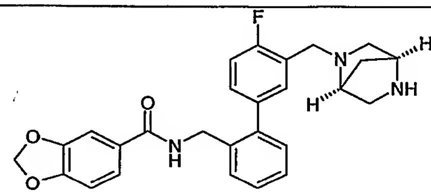
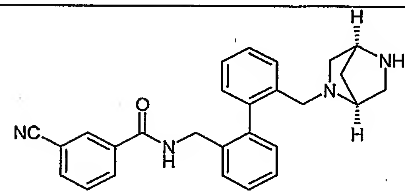
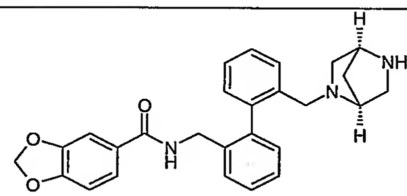
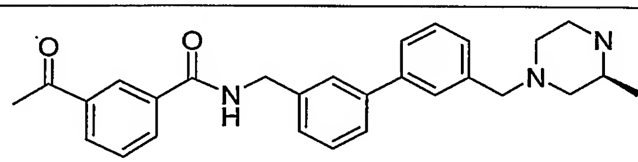
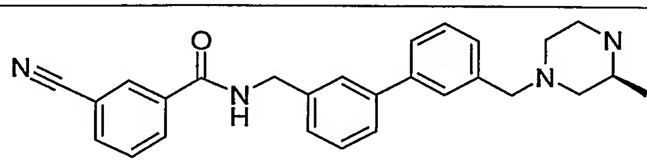
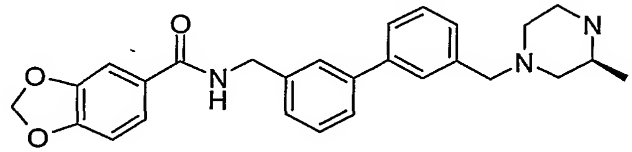
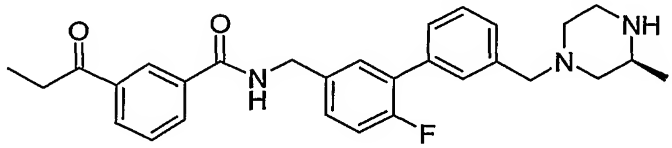
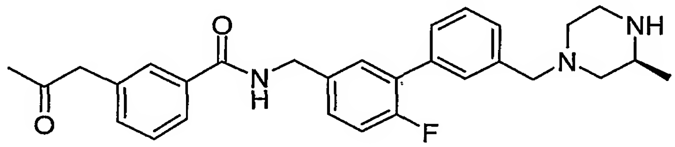
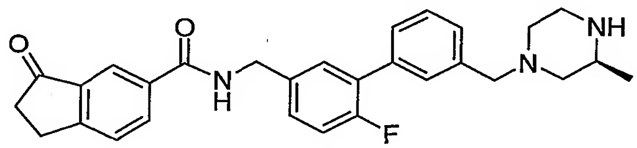
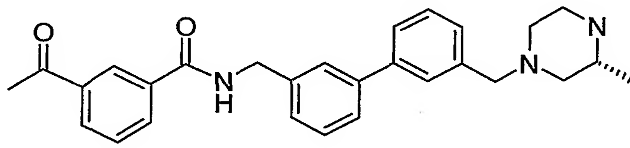
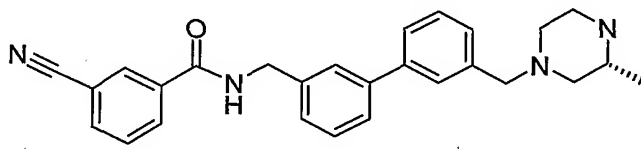
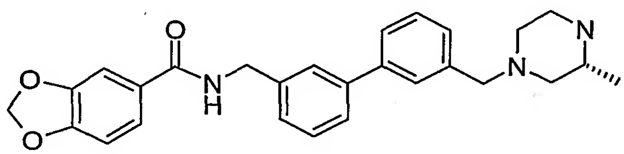
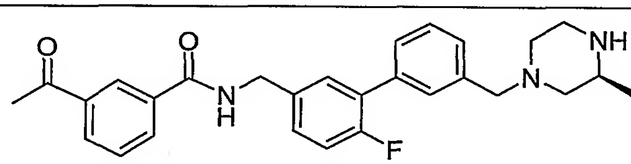
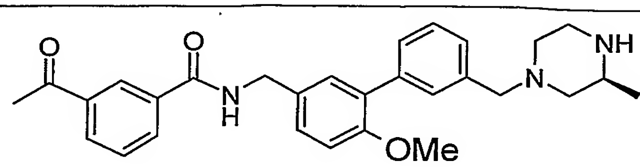
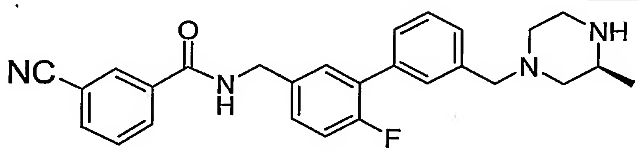
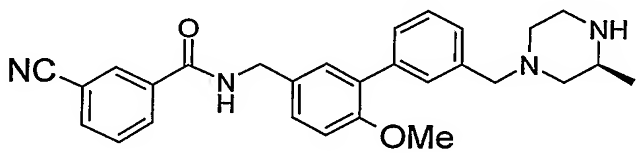
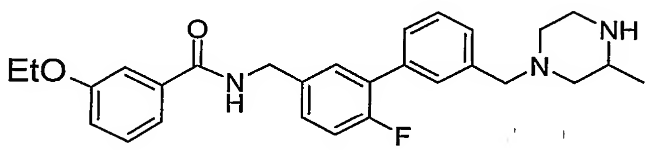
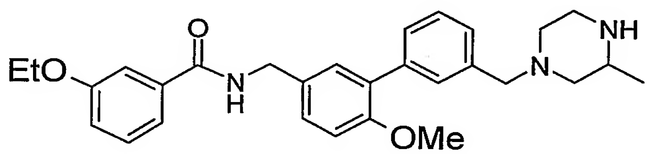
Example	Compound	MS [M+H]+
196		411
197		430
198		460
199		423
200		442

Table 13

Example	Compound	MS [M+H]+
201		442
202		425

203		444
204		474
205		474
206		472
207		442
208		425
209		444
210		460

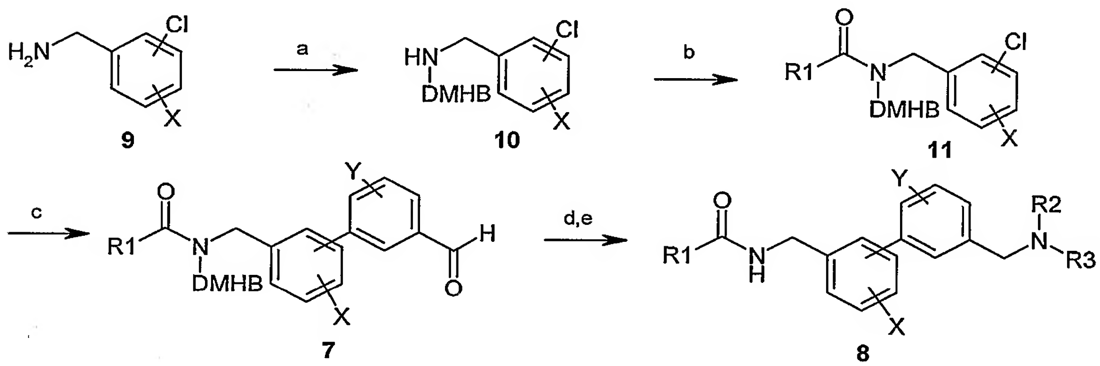
211		472
212		443
213		455
214		462
215		474

6-Carboxy-1-indanone used as the starting material of example **206** was prepared according to the following procedure: 3-(4-carboxyphenyl)propionic acid (5 g, 0.026 mol), frash $AlCl_3$ (25 g, 7.2 eq, 0.187 mol), and NaCl (2.5 g, 10% w/w of $AlCl_3$ used) were loaded into a 100 mL flask fitted with a condenser and internal thermometer going to the bottom of the flask. The flask was shaken briefly to mix the solids, then heated in an oil bath set to 190 °C. Internal temperature was held at or above 180° C for 1 h (reaction will fuse to form a dark brown liquid), then the mixture was cooled, and washed with water into a 2000 mL beaker containing ice. 180 mL of 6 M HCl and 250 mL of EtOAc were added. The layers were separated and the aqueous layer extracted with EtOAc (3 x 200 mL). Combined organic layers were washed with 2 M HCl, water, and brine, dried with $MgSO_4$, filtered and concentrated in *vacuo* to yield 6-carboxy-1-indanone (4.10 g, 90%) as a light brown solid directly used for the next step synthesis.

Preparation 3

Chloro substituted benzylamines **9** were loaded onto the DMHB resin (Scheme 3). The resin-bound amines **10** were reacted with acids to yield amides **11**, which underwent Suzuki coupling (using different conditions from **preparation 2**) to give biphenylaldehydes **7**. Reductive alkylation of **7** with amines, followed by cleavage, afforded the desired products **8**.

Scheme 3



Conditions: a) DMHB resin, $Na(OAc)_3BH$, HOAc, NMP, rt; b) $R1CO_2H$, DIC, DCM:DMF=1:1, rt; c) various formyl phenyl-boronic acids, $Pd(OAc)_2$, 2-(di-tert-butylphosphino)- biphenyl, KF, THF, 65 °C; d) NHR2R3, $Na(OAc)_3BH$, Na_2SO_4, DCE, rt; e) 50% of TFA in DCE, rt.

Example 216

Preparation of 3-cyano-*N*-{[6-fluoro-2'-(methyloxy)-5'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide

To a 50 mL shaker vessel was added 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde (DMHB resin) (2 g, 1.5 mmol/g, 3 mmol) and 25 mL of NMP. 3-Chloro-4-fluorobenzylamine (1.92 g, 12 mmol), HOAc (2.5 mL, 10%), and $Na(OAc)_3BH$ (3.18 g, 15 mmol) were then added. The mixture was shaken at rt for overnight. The resutling resin was washed with NMP (25 mL x 2), DCM (25 mL x 2), MeOH (25 mL x 2) and DCM (25 mL x 2) and dried in vacuum oven at 35 °C for overnight to yield DMHB resin-bound 3-chloro-4-fluorobenzylamine.

To amixture of the above resin (0.07 g, 1.2 mmol/g (theoretical loading), 0.084 mmol) in DCE:DMF (1:1, 3 mL) was added 3-cyanobenzoic acid (0.124 g,

0.84 mmol) and DIC (131 uL, 0.84 mmol). The mixture was shaken at rt for overnight. The resulting resin was washed with DMF (2 mL x 2), DCM (2 mL x 2), MeOH (2 mL x 2) and DCM (2 mL x 2), and dried in vacuum oven at 35 °C for overnight. An analytical amount of the resin was cleaved with 50% of TFA in DCE for 30 min. The resulting solution was concentrated *in vacuo* and dissolved in 0.5 mL of MeOH. MS (ESI): 289 $[M+H]^+$.

To a mixture of the above resin-bound *N*-[(3-chloro-4-fluorophenyl)methyl]-3-cyanobenzamide (0.081 g, 1.04 mmol/g (theoretical loading), 0.084 mmol) in 3 mL of THF was added $Pd(OAc)_2$ (0.015 g, 0.0672 mmol), 2-(di-tert-butylphosphino)biphenyl (0.040 g, 0.134 mmol), (5-formyl-2-methoxyphenyl)boronic acid (0.181 g, 1.01 mmol) and potassium fluoride (0.117 g, 2.016 mmol). The resulting mixture was purged with argon for 10 min and was then shaken at 65 °C for 16 h. The resin was washed with THF (2 mL x 2), THF:H_2O (1:1, 2 mL x 2), H_2O (2 mL x 2), THF:H_2O (1:1, 2 mL x 2), THF (2 mL x 2), DCM (2 mL x 2), and dried in vacuum oven at 35 °C for overnight. An analytical amount of the resin was cleaved with 50% of TFA in DCE for 30 min. The resulting solution was concentrated *in vacuo* and dissolved in 0.5 mL of CH_3CN. MS (ESI): 389 $[M+H]^+$.

To a mixture of the above resin-bound 3-cyano-*N*-{[6-fluoro-5'-formyl-2'-(methyloxy)-3-biphenylyl]methyl}benzamide (0.079 g, 0.94 mmol/g (theoretical loading), 0.084 mmol) in DCE (4 mL) was added Na_2SO_4 (0.06 g, 0.42 mmol) and 1,1-dimethylethyl 1-piperazinecarboxylate (0.078 g, 0.42 mmol). After shaking for 10 min, $Na(OAc)_3BH$ (0.107 g, 0.504 mmol) was added. The mixture was shaken at rt for overnight. The resulting resin was washed with THF (2 mL x 2), THF:H_2O (1:1, 2 mL x 2), H_2O (2 mL x 2), THF:H_2O (1:1, 2 mL x 2), THF (2 mL x 2), DCM (2 mL x 2), and dried in vacuum oven at 35 °C for overnight. The resin was cleaved with 2 mL of 50% of TFA in DCE for 30 min and treated again with 2 mL of 50% of TFA in DCE for 30 min. The combined cleavage solution was concentrated *in vacuo*. The residue was dissolved in DMSO and purified using a Gilson semi-preparative HPLC system with a YMC ODS-A (C-18) column 50 mm by 20 mm ID, eluting with 10% B to 90% B in 3.2 min, hold for 1 min where A = H_2O (0.1% trifluoroacetic acid) and B = CH_3CN (0.1% trifluoroacetic acid) pumped at 25 mL/min, to produce 3-cyano-*N*-{[6-fluoro-2'-(methyloxy)-5'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide as a bis-trifluoroacetate salt (white powder, 2.3 mg, 6% over 5 steps). MS (ESI): 459 $[M+H]^+$.

Proceeding in a similar manner, but replacing 3-cyanobenzoic acid with the appropriate acids, and/or replacing 1,1-dimethylethyl 1-piperazinecarboxylate with the appropriate amines, and/or replacing 3-chloro-4-fluorobenzylamine with appropriate chlorobenzylamines, and/or replacing 5-formyl-2-methoxyphenylboronic acid with appropriate formylphenyl boronic acids, the compounds listed in Tables 14 - 17 were prepared.

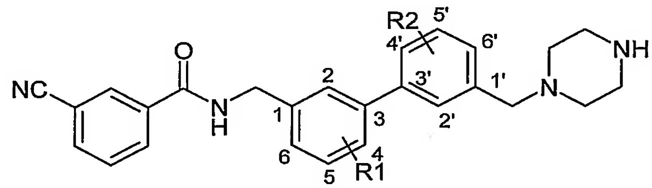


Table 14

Example	R1	R2	MS $[M+H]^+$
217	4-fluoro	4'-methoxy	459
218	4-fluoro	6'-fluoro	447
219	4-fluoro	6'-methoxy	459
220	4-methoxy	hydrogen	441
221	4-methoxy	4'-methoxy	471
222	4-methoxy	6'-fluoro	459
223	4-methoxy	6'-methoxy	471
224	6-methyl	hydrogen	425
225	6-fluoro	hydrogen	429
226	6-fluoro	4'-methoxy	459
227	6-fluoro	6'-fluoro	447
228	6-fluoro	6'-methoxy	459
229	2-fluoro	hydrogen	429

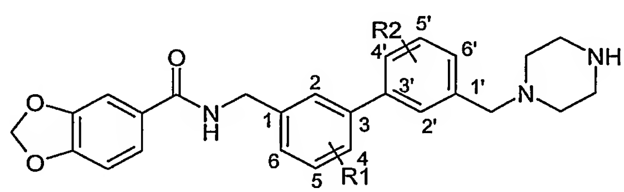


Table 15

Example	R1	R2	MS [M+H]+
230	4-fluoro	hydrogen	448
231	4-fluoro	4'-methoxy	478
232	4-fluoro	6'-fluoro	466
233	4-fluoro	6'-methoxy	478
234	4-methoxy	hydrogen	460
235	4-methoxy	6'-fluoro	459
236	4-methoxy	6'-methoxy	490
237	6-methyl	hydrogen	444
238	6-fluoro	hydrogen	448
239	2-fluoro	hydrogen	448
240	2-fluoro	6'-methoxy	478

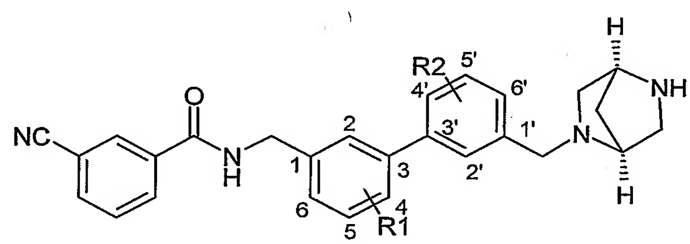


Table 16

Example	R1	R2	MS [M+H]+
241	4-fluoro	hydrogen	441
242	4-methoxy	hydrogen	453
243	6-fluoro	hydrogen	441
244	4-fluoro	6'-fluoro	459
245	4-methoxy	4'-methoxy	483
246	4-methoxy	6'-fluoro	471
247	4-methoxy	6'-methoxy	483
248	6-fluoro	4'-methoxy	471
249	6-fluoro	6'-fluoro	549
250	6-fluoro	6'-methoxy	471

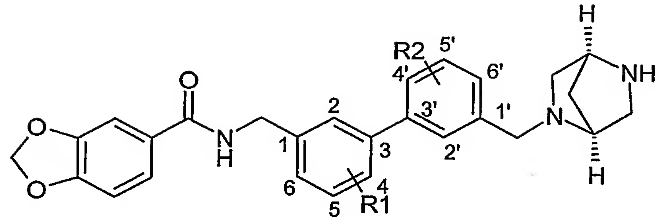


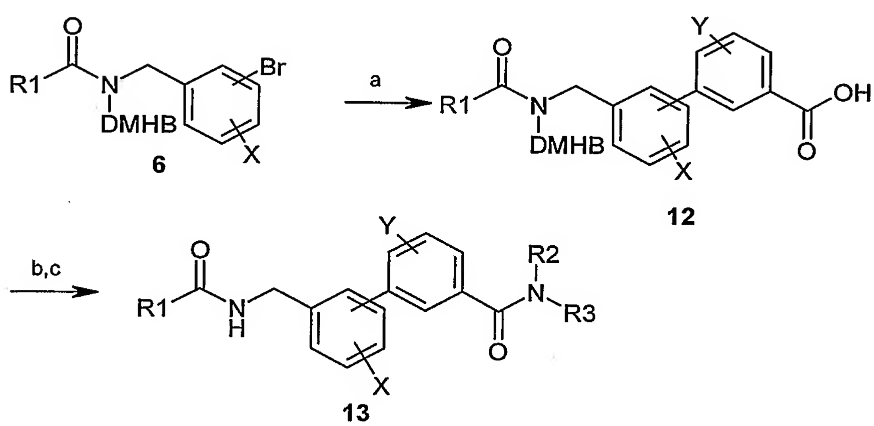
Table 17

Example	R1	R2	MS $[M+H]^+$
251	4-fluoro	hydrogen	460
252	4-methoxy	hydrogen	472
253	6-methyl	hydrogen	456
254	6-fluoro	hydrogen	460
255	2-fluoro	hydrogen	460
256	4-fluoro	4'-methoxy	490
257	4-fluoro	6'-fluoro	478
258	4-methoxy	6'-fluoro	490
259	6-fluoro	4'-methoxy	490

Preparation 4

Resin-bound bromo benzylamides **6** underwent Suzuki coupling with dihydroxyboranyl benzoic acids to give biaryl acides **12** (Scheme 4). Amide formation of **12** with amines, followed by cleavage, yielded the desired biaryl amides **13**.

Scheme 4



Conditions: a) dihydroxyboranyl benzoic acids, 10% $Pd(PPh_3)_4$, Cs_2CO_3, DMF, 80 °C; b) NHR2R3, PyBOP, DIEA, NMP, rt; c) 20% of TFA in DCM, rt.

Example 260

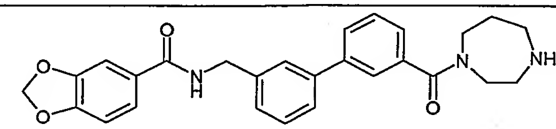
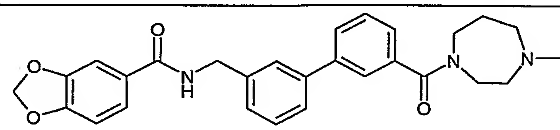
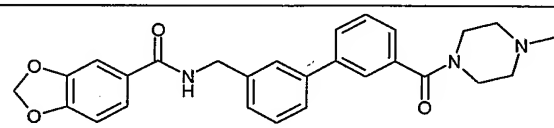
Preparation of *N*-{[3'-(1-piperazinylcarbonyl)-3-biphenylyl]methyl}-1,3-benzodioxole-5-carboxamide

To a mixture of DMHB resin-bound *N*-[(3-bromophenyl)methyl]-1,3-benzodioxole-5-carboxamide (**36a**, 1.3 g, 1.0 mmol/g (theoretical loading), 1.3 mmol) in 30 mL of DMF was added 3-(dihydroxyboranyl) benzoic acid (1.3 g, 7.8 mmol), 2 M $CsCO_3$ aqeous solution (1.95 mL, 3.9 mmol), and $Pd(PPh_3)_4$ (0.15 g, 0.13 mmol). The mixture was purged with argon for 5 min and was then heated at 80 °C for overnight. The resin was washed with DMF (50 mL), THF (50 mL x 2), THF:H_2O (1:1, 50 mL x 2), H_2O (50 mL x 2), THF:H_2O (1:1, 50 mL x 2), THF (50 mL x 2), DCM (50 mL x 2), and dried in vacuum oven at 35 °C for overnight. An analytical amount of the resin was cleaved with 20% of TFA in DCM for 10 min. The resulting solution was concentrated *in vacuo* and dissolved in 0.5 mL of MeOH. MS (ESI): 376 $[M+H]^+$.

To a mixture of the above resin bound 3'-{[(1,3-benzodioxol-5-ylcarbonyl)amino]methyl}-3-biphenylcarboxylic acid (80 mg, 0.97mmol/g (theoretical loading), 0.078 mmol) in 2.5 mL of NMP was added 1,1-dimethylethyl 1-piperazinecarboxylate (0.14 g, 0.75 mmol), DIEA (0.13 mL, 0.75 mmol), and PyBOP (0.2 g, 0.376 mmol). The mixture was shaken at rt for overnight. The resin was washed with NMP (10 mL x 2), DCM (10 mL x 2), MeOH (10 mL x 2), DCM (10 mL x 2), and dried in vacuum oven at 35 °C for overnight. The resin was cleaved with 2 mL of 20% of TFA in DCE for 30 min and treated againwith 2 mL of 20% of TFA in DCE for 30 min. The combined cleavage solution was concentrated *in vacuo*. The residue was dissolved in DMSO and purified using a Gilson semi-preparative HPLC system with a YMC ODS-A (C-18) column 50 mm by 20 mm ID, eluting with 10% B to 90% B in 3.2 min, hold for 1 min where A = H_2O (0.1% trifluoroacetic acid) and B = CH_3CN (0.1% trifluoroacetic acid) pumped at 25 mL/min, to produce *N*-{[3'-(1-piperazinylcarbonyl)-3-biphenylyl]methyl}-1,3-benzodioxole-5-carboxamide as a mono-trifluoroacetate salt (white powder, 8.5 mg, 25% over 5 steps). MS (ESI): 444 $[M+H]^+$.

Proceeding in a similar manner, but replacing 1,1-dimethylethyl 1-piperazinecarboxylate with the appropriate amines, the compounds listed in Table 18 were prepared.

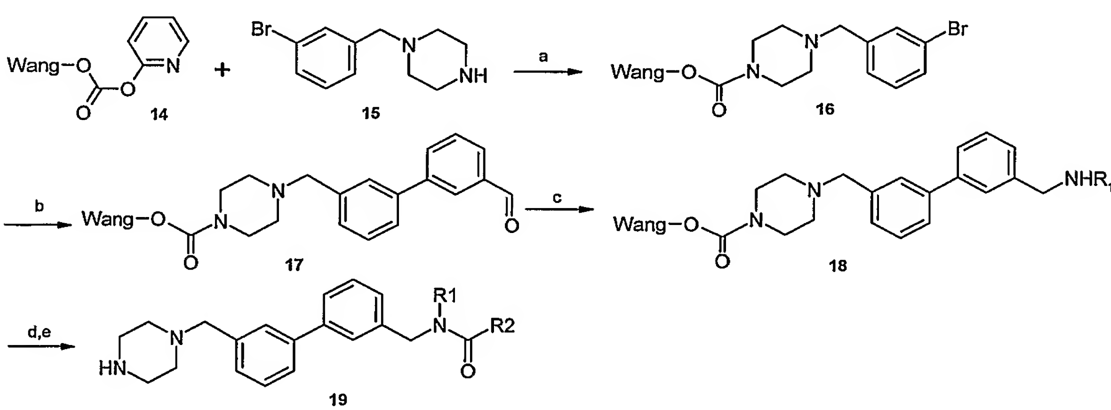
Table 18

Example	Compound	MS $[M+H]^+$
261		458
262		472
263		458

Preparation 5

1-(3-Bromobenzyl)piperazine (**15**) was loaded on activited Wang-resin **14** to form resin-bound bromide **16** which upon Suzuki coupling with 3-formyl benzeneboronic acid gave aldehyde **17** (Scheme 5). Reductive alkylation of **17** with primary amines afforded benzylamines **18**. Amide formation with acid chlorides, followed by resin cleavage, yielded N-alkylated benzylamides **19**.

Scheme 5



Conditions: a) DCM, rt; b) 3-formylbenzeneboronic acid, 8% $Pd(PPh_3)_4$, Na_2CO_3, DME, 80 °C; c) NH_2R1, $Na(OAc)_3BH$, Na_2SO_4, DCE, rt; d) R2COCl, triethylamine (TEA), DCM, rt; e) 20% of TFA in DCM, rt

Example 264

Preparation of *N*-cyclopropyl-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}octanamide

To a solution of N-Boc-piperazine (18.6 g, 0.1 mol) in dry dichloromethane (250 mL) was added with stirring 3-bromobenzaldehyde (19.43 g, 0.105 mol). After stirring under argon for 30 min, acetic acid (6.3 g, 0.105 mol) was added followed by solid sodium triacetoxyborohydride (25.4 g, 0.12 mol) portionwise over 20 min. to prevent excess warming and effervescence. The mixture was then stirred under argon for 18 h. Saturated $NaHCO_3$ solution was added cautiously with stirring until effervescence ceased, and the organic phase was separated, washed with $NaHCO_3$ solution and brine, then dried ($MgSO_4$) and evaporated in *vacuo*.

The oily product was dissolved in DCM (135 mL), and water (5 mL) was added. The solution was stirred whilst adding trifluroacetic acid (70 mL) portionwise with caution. Stirring was continued for 3.5 h, and the solution was then evaporated in *vacuo*. The residue was redissolved in DCM and stirred with saturated $NaHCO_3$ solution until effervescence ceased, and more $NaHCO_3$ solution was added until the solution became basic. The organic phase was separated, washed with $NaHCO_3$ solution, 2 M NaOH solution and brine, dried ($MgSO_4$) and evaporated in *vacuo* to produce 1-(3-Bromobenzyl)piperazine (**15**) as a pale brown oil (21.4 g, 84% over 2 steps); ^{1}H NMR, δ ($CDCl_3$) 1.84 (br s), 2.41 and 2.89 (each 4H, m) 3.45 (2H, s) 7.10-7.49 (4H, m). MS (ESI), 255 $[M+H]^+$.

Wang resin (15.9 g, 1.7 mmol.g^{-1}, 27 mmol) was suspended in anhydrous DCM and di-2-pyridylcarbonate and triethylamine were added. The mixture was shaken overnight under argon. The resin was filtered and washed 4 times with DCM then dried at room temperature in *vacuo* and used without further characterization.

Wang 2-pyridyl carbonate resin (**14**, 80 mmol) obtained from above was suspended in dry DCM (400 mL) and a solution of 1-(3-bromobenzyl)piperazine (**15**, 40.8 g, 160 mmol) in DCM (200 mL) was added. The mixture was shaken under argon for 24 h. The resin was filtered, washed with DCM (300 mL x 3), THF (300 mL x 3), DCM (300mL x 3), and ether (300 mL). The product resin was dried

in *vacuo*. A sample of the resin (**16**, 50 mg) was shaken with trifluoroacetic acid (0.2 mL) and DCM (0.8 mL) for 2 h. The resin was filtered and washed with DCM and methanol, and the filtrate evaporated to give the bis-trifluoroacetate salt of the amine **15** (26 mg, 93%); ^{1}H NMR, δ (CD_3OD) 3.05 (4H, m), 3.37(4H, m), 3.95 (2H, s), 7.35 (2H, m), 7.54 (1H, dd, J 1.5 and 6.2 Hz), 7.64 (1H, d, J 1.5 Hz). MS (ESI), 255 $[M+H]^+$.

The above resin **16** (22.0 g, 25.3 mmol) was suspended in 1,2-dimethoxyethane (DME) (500 mL) in a 3-neck 2 L flask fitted with an overhead stirrer. Argon was bubbled through the mixture for 30 min before adding tetrakis(triphenylphosphine) palladium (2.34 g, 2.03 mmol). 3-Formylbenzeneboronic acid (11.4 g, 76 mmol) was added followed by more DME (190 mL). A solution of Na_2CO_3 (16.1 g, 152 mmol) in water (76 mL) was then added and the mixture heated to 80 °C, whilst stirring under an argon atmosphere. After 16 h, the reaction mixture was cooled and the black resin product was filtered and washed with THF (500 mL), water (3 x 500 mL), THF:water (1:1, 2 x 500 mL), THF (3 x 500 mL), DCM (3 x 500 mL) and ether (2 x 500 mL). It was then dried at 40 °C in *vacuo* to afford product resin **17** (23.4 g).

The reductive alkylation reaction was performed in IRORI™ kans in a combinatorial process. The formyl resin **17** (30 mg) was placed in a kan containing a radiofrequency tag. In a mixture with other kans containing formyl resins, the kan was placed in a flask with 1,2-dichloroethane (1 mL/kan) and vacuum was applied and released to ensure that solvent filled the kan. 5 Equivalents each of sodium sulfate, cyclopropylamine and acetic acid were added to the flask which was purged with argon and then shaken for 3 h. Solid sodium triacetoxyborohydride was then added and shaking continued for a further 22 h. The kans were filtered and washed with THF, THF-water (1:1), water (x 2), THF-water (1:1), THF, water, DMF, methanol, THF (x 3) and DCM (x 3), and then dried in *vacuo* at 40 °C. The kan containing resin bound product **18** (R1 = cyclopropyl) was identified by reading the radiofrequency tag.

The kan containing resin product **18** (R1 = cyclopropyl) was reacted combinatorially in a mixture with kans containing other related amine resins. The kan was suspended in dry DCM (1 mL/kan) and vacuum applied and released to ensure filling of the kan with solvent. Triethylamine (12 eq) and octanoyl chloride (10 eq) were added and the mixture was shaken for 22 h. The kans were filtered and washed with DCM (x 2), THF, THF:water (1:1), THF (x 2) and DCM (x 3), and

then dried at 40 °C in *vacuo*. The kan containing the resin-bound product **19** (R1 = cyclopropyl, R2 = heptyl) was identified by reading the radiofrequency tag.

The kan containing the resin-bound product **19** (R1 = cyclopropyl, R2 = heptyl) was placed in a well of a cleavage block, and treated with a solution of 20% trifluoroacetic acid, 3% water, 77% DCM (2 mL). The block was gently agitated for 2 h, and the solution drained into a vial. The kan was washed with DCM:methanol (1:1, 1 mL), and the solution again drained into the vial. The solution in the vial was evaporated in a Genevac to produce N-cyclopropyl-N-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}octanamide as a bis-trifluoroacetate salt (7.6 mg, 28% over 5 steps). MS (ESI), 448 $[M+H]^+$.

Proceeding in a similar manner, but replacing cyclopropylamine with the appropriate amines, and/or replacing octanoyl chloride with the appropriate acid chlorides, the compounds listed in Table 19 were prepared.

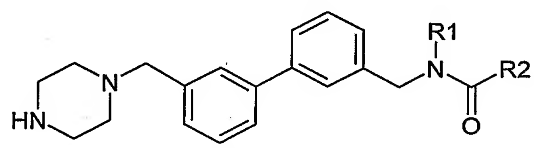


Table 19

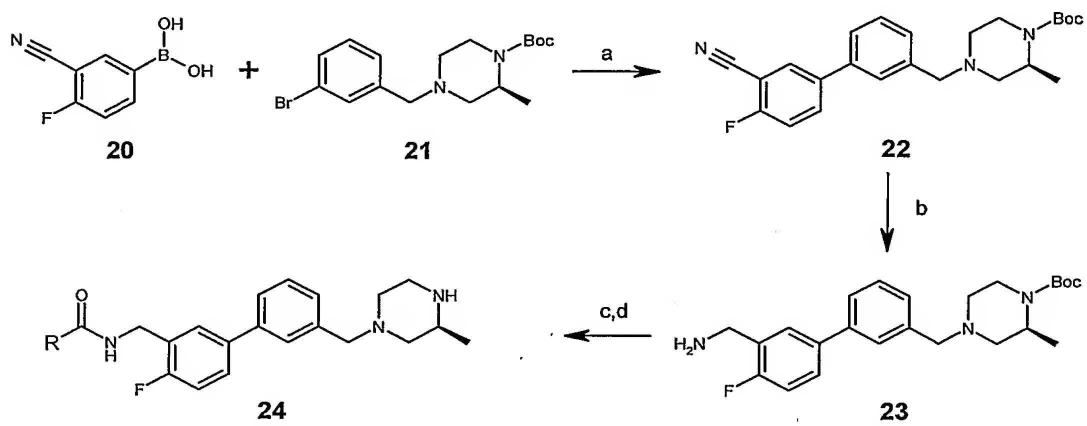
Example	R1	R2	MS $[M+H]^+$
265	2-(1-pyrrolidinyl)-ethyl	1-heptyl	505
266	2-(4-morpholinyl)-ethyl	1-heptyl	521
267	3-pyridinyl-methyl	1-heptyl	499
268	1-(phenylmethyl)-4-piperidinyl	1-heptyl	581
269	benzyl	1-heptyl	498
270	3,4-dichloro-benzyl	1-heptyl	566
271	4-methoxy-benzyl	1-heptyl	528
272	2-(*N*,*N*-dimethylamino)-ethyl	1-heptyl	479
273	3-phenylprop-1-yl	1-heptyl	526
274	3-(4-methyl-1-piperazinyl)-prop-1-yl	1-heptyl	548
275	3-(methyloxy)-prop-1-yl	1-heptyl	480
276	2-(2-thiophenyl)-ethyl	1-heptyl	518

277	3-(hydroxy)-3-oxo-prop-1-yl	1-heptyl	480
278	2-bromo-benzyl	1-heptyl	576
279	tetrahydro-2-furanyl-methyl	1-heptyl	492
280	cyclopropyl	3,4-methylenedioxy-phenyl	470
281	2-(1-pyrrolidinyl)-ethyl	3,4-methylenedioxy-phenyl	527
282	1-naphthyl-methyl	3,4-methylenedioxy-phenyl	570
283	2-(4-morpholinyl)-ethyl	3,4-methylenedioxy-phenyl	543
284	3-pyridinyl-methyl	3,4-methylenedioxy-phenyl	521
285	3-(trifluoromethyl)-benzyl	3,4-methylenedioxy-phenyl	588
286	2-(*N*,*N*-dimethylamino)-ethyl	3,4-methylenedioxy-phenyl	501
287	1-butyl	3,4-methylenedioxy-phenyl	486
288	3-(4-methyl-1-piperazinyl)-prop-1-yl	3,4-methylenedioxy-phenyl	570
289	3-(methyloxy)-prop-1-yl	3,4-methylenedioxy-phenyl	502
290	3-(hydroxy)-3-oxo-prop-1-yl	3,4-methylenedioxy-phenyl	502
291	2-bromo-benzyl	3,4-methylenedioxy-phenyl	598
292	3-methoxy-phenethyl	3,4-methylenedioxy-phenyl	564
293	tetrahydro-2-furanyl-methyl	3,4-methylenedioxy-phenyl	514

Preparation 6

The 4-fluoro-derivatives of general structure **24** were prepared in solution phase following the route outlined in Scheme 6. Firstly, the boronic acid **20** underwent a Suzuki palladium coupling with the bromide **21** to give the 4-fluoro-biphenyl derivative **22**. Further reduction of the nitrile moiety with borane yielded the primary amine **23**. Subsequent coupling of **23** to the appropriate benzoic acids gave the respective products **24**.

Scheme 6



Conditions: a) $Pd(PPh_3)_4$, Na_2CO_3, DME, 78 °C; b) BH_3, THF; c) HATU, RCO_2H, DIPEA, DMF; d) HCl.

Example 294

Preparation of 3-cyano-*N*-[(4-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide

1,1-Dimethylethyl (2S)-4-[(3'-cyano-4'-fluoro-3-biphenylyl)methyl]-2-methyl-1-piperazinecarboxylate

To a solution of (3-cyano-4-fluorophenyl)boronic acid (0.983 g, 5.96 mmol) in DME (40 mL) was added 1,1-dimethylethyl (2*S*)-4-[(3-bromophenyl)methyl]-2-methyl-1-piperazinecarboxylate (2.20 g, 5.96 mmol) followed by Na_2CO_3 (17 mL, 2M in H_2O, 34.0 mmol). The reaction vessel was flushed with argon, and tetrakis(triphenylphosphine)palladium(0) (2.06 g, 1.78 mmol) was added. The reaction mixture was placed in an oil bath at 78 °C under argon for overnight. The reaction was diluted with EtOAc (600 mL) and washed with H_2O (250 mL). The

water layer was extracted with EtOAc (1 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. Purification of the crude residue by flash chromatography (20% EtOAc / 80% hexane) on silica gel gave the title compound (1.77 g, 73.1%). EI-MS m/z 410$(M-H)^+$.

1,1-Dimethylethyl (2S)-4-{[3'-(aminomethyl)-4'-fluoro-3-biphenylyl]methyl}-2-methyl-1-piperazinecarboxylate

A solution of 1,1-dimethylethyl (2S)-4-[(3'-cyano-4'-fluoro-3-biphenylyl)methyl]-2-methyl-1-piperazinecarboxylate (2.29 g, 5.59 mmol) in THF (50 mL) was flushed with argon. Borane (19 mL, 1M in THF, 19 mmol) was slowly added and the reaction was allowed to stir at room temperature overnight. The reaction was quenched slowly with water, diluted with water (175 mL) and then extracted with EtOAc (2 x 250 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was placed onto a SPE silica cartridge (20 g) using 50% hexane/ 50% EtOAc, and then eluted with the following sequence: 50% hexane/ 50% EtOAc, 10% MeOH/ 90% DCM, 30% MeOH/ 70% DCM. The product fractions were combined and concentrated to give the title compound (1.48 g, 64.1%). EI-MS m/z 414$(M-H)^+$.

General procedure for amide formation and Boc deprotection

3-cyano-N-[(4-fluoro-3'-{[(3S)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide

To a solution of 1,1-dimethylethyl (2S)-4-{[3'-(aminomethyl)-4'-fluoro-3-biphenylyl]methyl}-2-methyl-1-piperazinecarboxylate (0.100 g, 0.242 mmol) in DMF (2.5 mL) were added 3-cyanobenzoic acid (0.038 g, 0.260 mmol), HATU (0.102 g, 0.268 mmol), and diisopropylethylamine (0.10 mL, 0.574 mmol). The reaction was allowed to stir at room temperature for 2 days. The reaction was diluted with EtOAc (75 mL), washed with 1N HCl (2 x 20 mL), saturated $NaHCO_3$ (3 x 20 mL), then brine (2 x 20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was taken up in MeOH (4 mL) and HCl (4N in 1,2-dioxane, 2.5 mL) was added. The reaction was allowed to stir at room temperature overnight. The reaction was concentrated under vacuum, and the residue was taken up in 1 mL DMSO/ 1 mL MeOH and purified via MDAP (10-90% CH_3CN/ H_2O/ (0.1% TFA)). The desired fractions were isolated, and then taken up

in DCM (8 mL) and 1N NaOH (8 mL) and allowed to stir for 1 hour. The DCM was isolated using a phase separator and then concentrated under vacuum to give the title compound (96 mg, 90%). EI-MS m/z 443(M-H)$^+$.

Example 295

Preparation of *N*-[(4-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-3-(phenylcarbonyl)benzamide

Following the general procedure outlined in Example **294**, 1,1-dimethylethyl (2S)-4-{[3'-(aminomethyl)-4'-fluoro-3-biphenylyl]methyl}-2-methyl-1-piperazinecarboxylate (0.095 g, 0.231 mmol), 3-(phenylcarbonyl)benzoic acid (0.058 g, 0.255 mmol), HATU (0.102 g, 0.268 mmol), and diisopropylethylamine (0.10 mL, 0.574 mmol) in DMF (2.5 mL) were reacted to give the desired product (0.045g, 37.4%). EI-MS m/z 522(M-H)$^+$.

Example 296

Preparation of *N*-[(4-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-1,3-benzodioxole-5-carboxamide

Following the general procedure outlined in Example **294**, 1,1-dimethylethyl (2S)-4-{[3'-(aminomethyl)-4'-fluoro-3-biphenylyl]methyl}-2-methyl-1-piperazinecarboxylate (0.098 g, 0.235 mmol), 1,3-benzodioxole-5-carboxylic acid (0.039 g, 0.235 mmol), HATU (0.107 g, 0.280 mmol), and diisopropylethylamine (0.10 mL, 0.574 mmol) in DMF (2.5 mL) were reacted to give the desired product (0.043g, 40.1%). EI-MS m/z 462(M-H)$^+$.

Example 297

Preparation of 3-(ethyloxy)-*N*-[(4-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide

Following the general procedure outlined in Example **294**, 1,1-dimethylethyl (2S)-4-{[3'-(aminomethyl)-4'-fluoro-3-biphenylyl]methyl}-2-methyl-1-piperazinecarboxylate (0.099 g, 0.240 mmol), 3-(ethyloxy)benzoic acid (0.042 g, 0.253 mmol), HATU (0.103 g, 0.271 mmol), and diisopropylethylamine (0.10 mL, 0.574 mmol) in DMF (2.5 mL) were reacted to give the desired product (0.037g, 33.7%). EI-MS m/z 462(M-H)$^+$.

Example 298

Preparation of 3-acetyl-*N*-[(4-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide

Following the general procedure outlined in Example **294**, 1,1-dimethylethyl (2S)-4-{[3'-(aminomethyl)-4'-fluoro-3-biphenylyl]methyl}-2-methyl-1-piperazinecarboxylate (0.100 g, 0.242 mmol), 3-acetylbenzoic acid (0.044 g, 0.269 mmol), HATU (0.104 g, 0.274 mmol), and diisopropylethylamine (0.10 mL, 0.574 mmol) in DMF (2.5 mL) were reacted to give the desired product (0.039g, 35.4%). EI-MS m/z 460(M-H)$^+$.

Example 299

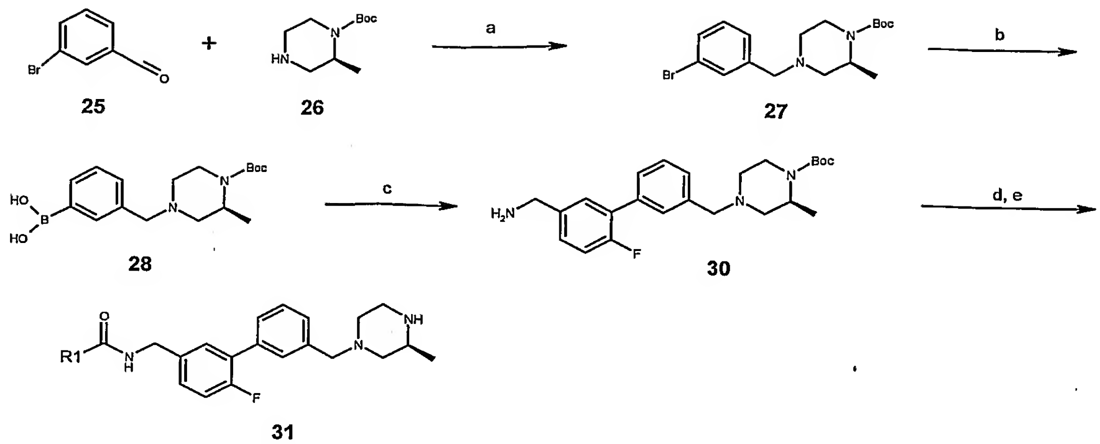
Preparation of 3-[(3,4-dichlorophenyl)carbonyl]-*N*-[(4-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide

Following the general procedure outlined in Example **294**, 1,1-dimethylethyl (2S)-4-{[3'-(aminomethyl)-4'-fluoro-3-biphenylyl]methyl}-2-methyl-1-piperazinecarboxylate (0.108 g, 0.261 mmol), 3-[(3,4-dichlorophenyl)carbonyl]benzoic acid (0.074 g, 0.251 mmol), HATU (0.110 g, 0.290 mmol), and diisopropylethylamine (0.10 mL, 0.574 mmol) in DMF (2.5 mL) were reacted to give the desired product (0.1095g, 76.0%). EI-MS m/z 590(M-H)$^+$.

Preparation 7

Scheme 7 outlines a solution phase route to synthesize compounds with structure **31**. Reductive amination of the benzaldehyde **25** with the BOC-protected pierazine **26** gave the tertiary amine **27**. Boronation using trimethyl borate led to the boronic acid **28**. Further Suzuki coupling of **28** with the commercially available bromide **29** produced compound **30**, which in turn could be coupled with the appropriate carbocylic acid R_1CO_2H or acyl halide and deptrotected to furnish the products **31**.

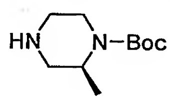
Scheme 7



Conditions: a) $NaB(OAc)_3H$, DCM, rt, b) nBuLi, $B(OMe)_3$, -78 °C to rt; c) (3-bromo-4-fluorophenyl)methyl amine (**29**), $Pd(PH_3)_4$, K_2CO_3, mw, 150 °C, 20 min.; d) R_1CO_2H, TEA, EDC, TEA, HOBt in $CHCl_3$ or R_1COCl, TEA, DCM; e) TFA.

Intermediate 26

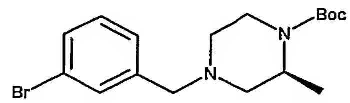
1,1-dimethylethyl (2S)-2-methyl-1-piperazinecarboxylate



A solution of (S)-2-methyl piperazine (2 g, 20 mmol) in THF (200 mL) was mixed with *n*-BuLi (25 mL, 1.6 M in hexane, 40 mmol) at rt. The solution was stirred for 30 min before TBDMSCl (3.04 g, 20 mmol) was added. The mixture was stirred for an additional hour and $(Boc)_2O$ (5.2 g, 24 mmol) was added to the solution. The resulting mixture was stirred for another hour and diluted with H_2O (50 mL). The organic layer was separated, washed with brine (50 mL), dried over Na_2SO_4 and concentrated under vacuum. Flash chromatography on silica (5% MeOH / 2% NH_4OH / 93% CH_2Cl_2) then provided the title compound as a yellow oil (3.7 g, 93%). LC/MS: m/z, 201(M+H); ^{1}HNMR($CDCl_3$) 1.26(3H, d), 1.49(9H, s), 2.1(1H, s), 2.7(1H, m), 2.85(1H, m), 3.0 (3H, m), 3.8 (1H, m), 4.2(1H, m).

Intermediate 27

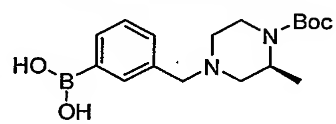
1,1-dimethylethyl (2*S*)-4-[(3-bromophenyl)methyl]-2-methyl-1-piperazine carboxylate



A solution of 1,1-dimethylethyl (2*S*)-2-methyl-1-piperazinecarboxylate (Intermediate **26**, 100 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) was mixed with 3-bromo benzaldehyde (0.06 mL, 0.5 mmol) and $NaB(OAc)_3H$ (0.16 g, 0.75 mmol). The resulting mixture was stirred for 12 hours, diluted with dichloromethane (30 mL) and washed with brine (50 mL). The organic layer was collected, dried over Na_2SO_4 and concentrated. Separation via a combiflash system then afforded the title compound (150 mg, 81%). LC/MS: m/z, 369 (M+H); ^{1}HNMR(MeOD) 1.26(3H, d), 1.47(9H, s), 2.0(1H, m), 2.1(1H, m), 2.6(1H, m), 2.8(1H, m), 3.1(1H, m), 3.3(2H, s), 3.4(1H, m), 3.5(1H, m), 3.8(1H, m), 4.2(1H, m), 4.88(1H, s), 7.25(1H, m), 7.3(1H, m), 7.4(1H, m), 7.55(1H, s).

Intermediate 28

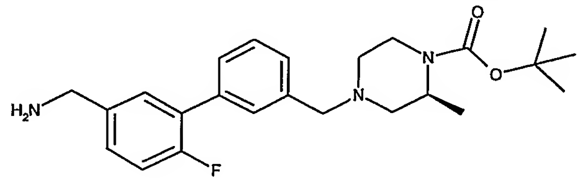
{3-[((3*S*)-4-{[(1,1-dimethylethyl)oxy]carbonyl}-3-methyl-1-piperazinyl)methyl]phenyl} boronic acid



A solution of 1,1-dimethylethyl (2S)-4-[(3-bromophenyl)methyl]-2-methyl-1-piperazine carboxylate (Intermediate 27, 1.8 g, 4.9 mmol) in THF (4.9 mL) was mixed with *n*-BuLi (3.7 mL, 1.6 M in Hexane, 5.9 mmol) at –78 °C and stirred for 30 min before $B(OMe)_3$ (2.2 mL, 19.6 mmol) was added. After addition, the resulting solution was warmed up to room temperature within 2 hours. The mixture was then mixed with saturated aqueous NH_4Cl solution (10 mL), stirred for 25 minutes at room temperature, diluted with H_2O (5 mL) and extracted with Et_2O (2 X 30 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated to afford the crude title compound (1.7 g, quantitative yield). LC/MS: m/z 335 (M+H); ^{1}H-NMR(MeOD) δ 1.24 (d, 3H), 1.46 (s, 9H), 2.00 (m, 1H), 2.13 (m, 1H), 2.68 (d, 1H), 2.82 (d, 1H), 3.12 (m, 1H), 3.44 (m, 1H), 3.56 (m, 1H), 3.80 (d, 1H), 4.18 (m, 1H), 7.33 (m, 1H), 7.38 (m, 1H), 7.51 (d, 1H), 7.59 (s, 1H).

Intermediate 30

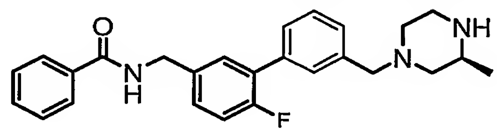
1,1-dimethylethyl(2*S*)-4-{[5'-(aminomethyl)-2'-fluoro-3-biphenylyl]methyl}-2-methyl-1-piperazinecarboxylate



To a solution of [(3-bromo-4-fluorophenyl)methyl]amine hydrochloride (1.68 g, 7 mmol) in dioxane/H_2O (10 mL/3.3 mL) were added {3-[((3*S*)-4-{[(1,1-dimethylethyl)oxy]carbonyl}-3-methyl-1-piperazinyl)methyl]phenyl} boronic acid (intermediate **28**, 2.33 g, 7 mmol), K_2CO_3 (4.83, 35 mmol) and $Pd(PPh_3)_4$ (405 mg, 0.35 mmol). The resulting mixture was heated at 150 °C in a pressure vessel for 2 hours, then cooled to rt and diluted with EtOAc (50 mL). The organic layer was collected and the aqueous layer was extracted by EtOAc (30 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The residue was purified by Gilson preparatory HPLC, eluting with acetonitrile/water/0.1%TFA (10/90 to 90/10, v/v, over 12 min), to give the title compound (1.08 g, 37%). LC/MS: m/z, 414 (M+H), 1.83 min.

Example 300

***N*-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide**

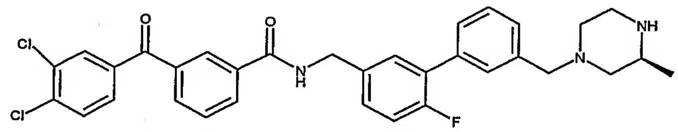


To a solution of 1,1-dimethylethyl (2*S*)-4-{[5'-(aminomethyl)-2'-fluoro-3-biphenylyl]methyl}-2-methyl-1-piperazinecarboxylate (Intermediate **30**, 60 mg, 0.145 mmol) in 5 mL of DCM, was added benzoyl chloride (55 mg, 0.16 mmol), followed by addition of TEA (0.05 mL, 0.3 mmol). The reaction mixture was stirred at room temperature for 1 h, and quenched by addition of 0.5 mL of saturated Na_2CO_3. The organic layer was isolated via a hydrophobic frit followed by addition of 0.5 mL of TFA. The mixture was stirred at room temperature for 1 h. After removal of the solvent, the residue was purified by Gilson reverse phase HPLC, eluting with

acetonitrile/water/0.1%TFA (10/90 to 70/30, v/v, over 12 min), to give the title compound (16 mg, 12%). LC/MS: m/z, 417 (M+H), 1.58 min.

Example 301

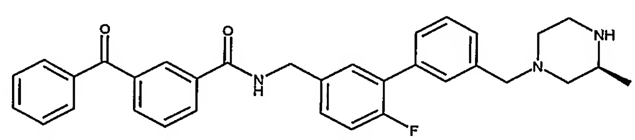
3-[(3,4-dichlorophenyl)carbonyl]-*N*-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide



To a solution of [(3,4-dichlorophenyl)carbonyl]benzoic acid (36 mg, 0.121 mmol in $CHCl_3$ (2.0 mL) were added 1,1-dimethylethyl (2*S*)-4-({6-[3-(aminomethyl)phenyl]-2-pyridinyl}methyl)-2-methyl-1-piperazinecarboxylate (Intermediate **30**, 50 mg, 0.13 mmol), TEA (0.04 ml, 0.3 mmol), EDC (36 mg, 0.19 mmol) and HOBt (18 mg, 0.14 mmol). The reaction mixture was stirred at room temperature for 2 h, then 0.5 mL of a saturated Na_2CO_3 solution was added. The organic layer was isolated via a hydrophobic frit followed by addition of 0.5 mL of TFA, and stirred at room temperature for 1 h. After removal of the solvent, the residue was purified by Gilson reverse phase HPLC, eluting with acetonitrile/water/0.1%TFA (10/90 to 70/30, v/v, over 12 min.), to give the title compound (26 mg, 36%). LC/MS: m/z, 590 (M+H), 1.66 min.

Example 302

***N*-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-3-(phenylcarbonyl)benzamide**



To a solution of 1,1-dimethylethyl (2*S*)-4-({6-[3-(aminomethyl)phenyl]-2-pyridinyl}methyl)-2-methyl-1-piperazinecarboxylate (Intermediate **30**, 50 mg, 0.13 mmol) in $CHCl_3$ (5 mL) were added 3-(phenylcarbonyl)benzoic acid (1.5eq), EDC (12 mg, 0.06 mmol), HOBT (1 mg, 0.006 mmol) and diisopropyl ethyl amine (0.1 mL). The resulting mixture was stirred for 12 hours and then concentrated in *vacuo*. Separation via a combiflash system then provided the desired amide. The amide was dissolved in CH_2Cl_2 (2 mL) and the solution was mixed with TFA (0.7 mL) at 0 °C. The mixture was stirred at ambient temperature overnight, diluted with

Et_3N (0.1 mL) at –78 °C and concentrated. Separation via a Gilson reverse phase HPLC then provided the title compound (60 mg, 99%). LC/MS(ES) *m/z* 523 $(M+H)^+$; ^{1}HNMR(MeOD) 1.37(3H, d), 3.05(1H, m), 3.24(1H, m), 3.46(1H, m), 3.66(4H, m), 4.37(2H, s), 4.62(2H, s), 7.19(1H, t), 7.43(1H, m), 7.56(5H, m), 7.66(3H, m), 7.72(1H,s), 7.78(2H, d), 7.93(1H, d), 8.14(1H, d), 8.3(1H, s).

The compounds listed in Table 20 were prepared proceeding in a similar manner to Example **302**, but replacing 3-(phenylcarbonyl)benzoic acid with the appropriate acids.

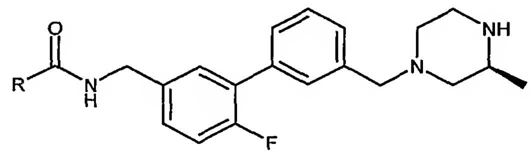
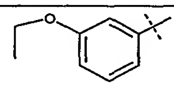
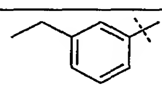


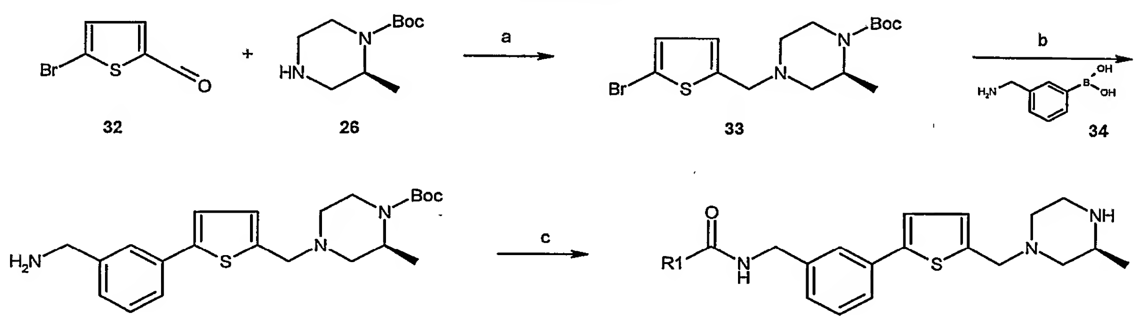
Table 20

Example	R	MS [MH]+	NMR
303		462	^{1}HNMR(MeOD) 1.41(6H, m), 3.13(1H, t), 3.33(1H, m), 3.45(1H, m), 3.68(4H, m), 4.07(2H, q), 4.40(2H, s), 4.60(2H, s), 7.08(1H, t), 7.19(1H, t), 7.43(4H, m), 7.53(3H, m), 7.66(1H, m), 7.73(1H, s).
304		447	^{1}HNMR(MeOD) 1.28(3H, t), 1.39(3H, d), 2.72(2H, t), 3.08(1H, m), 3.25(1H, m), 3.46(1H, m), 3.67(4H, m), 4.36(2H, s), 4.61(2H, s), 7.20(1H, t), 7.44(3H, m), 7.55(3H, m), 7.66(2H, m), 7.72(2H, m).

Preparation 8

The thiophene derivatives of general structure **36** were prepared as depicted in Scheme 8. Reductive amination of the thiophene carboxaldehyde derivative **32** with the BOC-protected pierazine **26** gave the tertiary amine **33**. Further palladium coupling of **33** with the commercially available boronic acid **34** produced compound **35**, which in turn could be coupled with the appropriate carboxylic acids R_1CO_2H to furnish the products **36**.

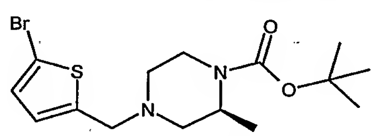
Scheme 8



Conditions: a) $NaB(OAc)_3H$, DCM, rt, b)$Pd(PH_3)_4$, K_2CO_3, mw, 150 °C, 20 min.; c) R_1CO_2H, TEA, EDC, TEA, HOBt in $CHCl_3$ then TFA.

Intermediate 33

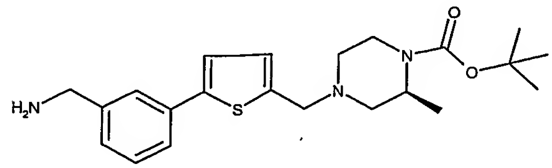
1,1-Dimethylethyl (2*S*)-4-[(5-bromo-2-thienyl)methyl]-2-methyl-1-piperazinecarboxylate



Following the standard procedure outlined for intermediate **27**, 1,1-dimethylethyl (2*S*)-2-methyl-1-piperazinecarboxylate **26** (1.0 g, 5 mmol) was reacted with 5-bromo-2-thiophenecarbaldehyde **32** (0.96 g, 5 mmol) to give the title compound (1.43 g, 76%). LCMS: m/z, 375 (M+H), 1.63 min.

Intermediate 35

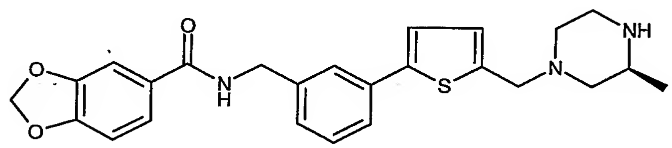
1,1-dimethylethyl (2*S*)-4-({5-[3-(aminomethyl)phenyl]-2-thienyl}methyl)-2-methyl-1-piperazinecarboxylate



To the solution of [3-(aminomethyl)phenyl]boronic acid hydrochloride **34** (325 mg, 1.2 mmol) in dioxane/H_2O (10 mL/3.3 mL) was added (2*S*)-4-[(5-bromo-2-thienyl)methyl]-2-methyl-1-piperazinecarboxylate (intermediate **33**, 450 mg, 1.2 mmol), K_2CO_3 (828 mg, 6.0 mmol) and $Pd(PPh_3)_4$ (70 mg, 0.06 mmol). The resulting solution was irradiated in a microwave reactor at 150 °C for 20 minutes and diluted with EtOAc (5 mL). The organic layer was collected and the aqueous layer was extracted by EtOAc (2 X 5 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The residue was purified by Gilson HPLC, eluting with acetonitrile/water/0.1%TFA (10/90 to 90/10, v/v, over 12 min), to give the title compound (200 mg, 42%). LC/MS: m/z, 402 (M+H), 1.24 min.

Example 305

***N*-{[3-(5-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-2-thienyl)phenyl]methyl}-1,3-benzodioxole-5-carboxamide**



To a solution of 1,3-benzodioxole-5-carboxylic acid (12 mg, 0.075 mmol) in $CHCl_3$ (3.0 mL) were added 1,1-dimethylethyl (2*S*)-4-({5-[3-(aminomethyl)phenyl]-2-thienyl}methyl)-2-methyl-1-piperazinecarboxylate (intermediate **35**, 30 mg, 0.075 mmol), TEA (0.05 ml, 0.4 mmol), EDC (22 mg, 0.113 mmol) and HOBt (11 mg, 0.083 mmol). The reaction mixture was stirred at room temperature for 15 h, followed by addition of 1 mL of saturated Na_2CO_3. The organic layer was dried over Na_2SO_4 and filtered. The filtrate was mixed with 1 mL of TFA, and stirred at room temperature for 1 h. After removal of the solvent, the residue was purified by Gilson reverse phase HPLC, eluting with acetonitrile/water/0.1%TFA (10/90 to 70/30, v/v,

over 12 min), to give the title compound (31 mg, 73%). LC/MS: m/z, 350 (M+H), 1.58 min.

The compounds listed in Table 21 were prepared proceeding in a similar manner to Example **305**, but replacing 1,3-benzodioxole-5-carboxylic acid with the appropriate acids.

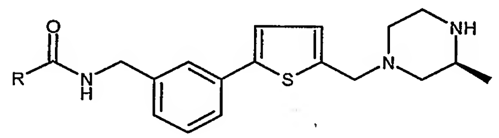
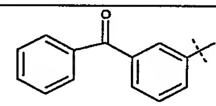
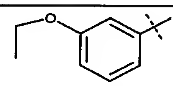
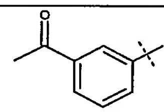


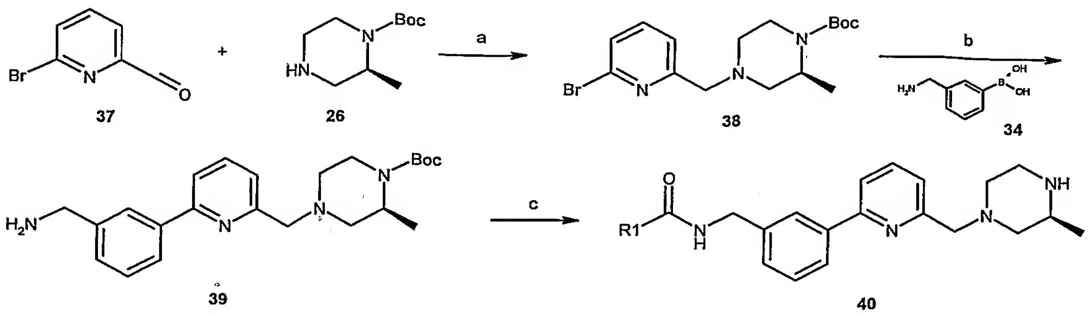
Table 21

Example	R	MS [MH]+	Rt (min)
306		510	1.74
307		450	1.62
308		448	1.48

Preparation 9

The pyridine derivatives of general structure **40** were prepared as depicted in Scheme 9. Reductive amination of the pyridine carboxaldehyde derivative **37** with the BOC-protected pierazine **26** gave the tertiary amine **38**. Further palladium coupling of **38** with the commercially available boronic acid **34** produced compound **39**, which in turn could be coupled with the appropriate carboxylic acid R_1CO_2H to furnish the products **40**.

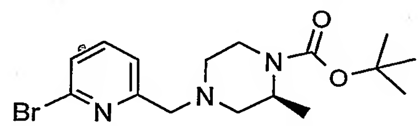
Scheme 9



Conditions: a) $NaB(OAc)_3H$, DCM, rt, b)$Pd(PH_3)_4$, K_2CO_3, mw, 150 °C, 20 min.; c) R_1CO_2H, TEA, EDC, TEA, HOBt in $CHCl_3$ then TFA.

Intermediate 38

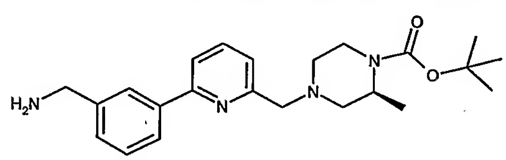
1,1-dimethylethyl (2*S*)-4-[(6-bromo-2-pyridinyl)methyl]-2-methyl-1-piperazinecarboxylate



Following the standard procedure outlined for intermediate **27**, 1,1-dimethylethyl (2*S*)-2-methyl-1-piperazinecarboxylate **26** (1.0 g, 5 mmol) was reacted with 5-bromo-2-thiophenecarbaldehyde **37** (0.96 g, 5 mmol) to give the title compound (1.43 g, 76%). LC/MS: m/z, 375 (M+H), 1.63 min.

Intermediate 39

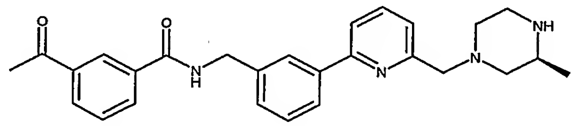
1,1-dimethylethyl (2*S*)-4-({6-[3-(aminomethyl)phenyl]-2-pyridinyl}methyl)-2-methyl-1-piperazinecarboxylate



Following the standard procedure outlined for intermediate **35**, 1,1-dimethylethyl (2*S*)-4-[(6-bromo-2-pyridinyl)methyl]-2-methyl-1-piperazinecarboxylate (Intermediate **38**, 430 mg, 1.16 mmol) was reacted with [3-(aminomethyl)phenyl]boronic acid **34** (314 mg, 1.16 mmol) to give the title compound (420 mg, 92%). LC/MS: m/z, 397 (M+H), 1.22 min.

Example 309

3-acetyl-*N*-{[3-(6-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-2-pyridinyl)phenyl]methyl}benzamide



To a solution of 3-acetylbenzoic acid (21 mg, 0.13 mmol) in $CHCl_3$ (2.0 mL) were added 1,1-dimethylethyl (2*S*)-4-({6-[3-(aminomethyl)phenyl]-2-pyridinyl}methyl)-2-methyl-1-piperazinecarboxylate (intermediate **39**, 50 mg, 0.13 mmol), TEA (0.04 mL, 0.3 mmol), EDC (36 mg, 0.19 mmol) and HOBt (18 mg, 0.14 mmol). The reaction mixture was stirred at room temperature for 2 h, followed by addition of 0.5 mL of saturated Na_2CO_3. The organic layer was isolated via a hydrophobic frit followed by addition of 0.5 mL of TFA, and stirred at room temperature for 1 h. After removal of the solvent, the residue was purified by Gilson reverse phase HPLC, eluting with acetonitrile/water/0.1%TFA (10/90 to 70/30, v/v, over 12 min), to give the title compound (10 mg, 10%). LC/MS: m/z, 443 (M+H), 1.20 min.

The compounds listed in Table 22 were prepared proceeding in a similar manner to **Example 309**, but replacing 3-acetylbenzoic acid with the appropriate acid.

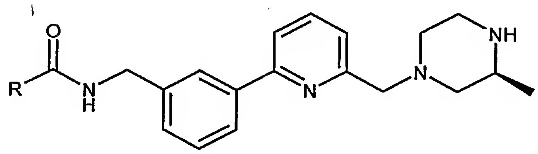
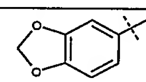
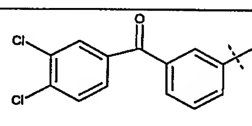
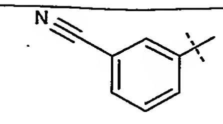
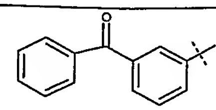
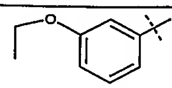


Table 22

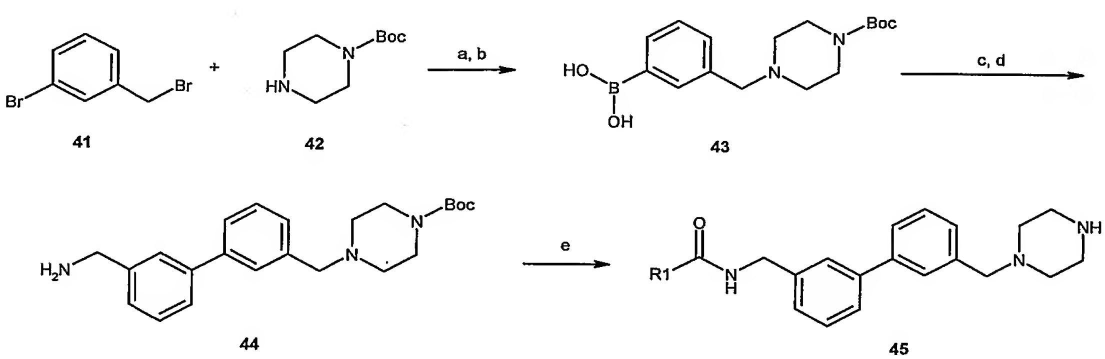
Example	R	MS [MH]+	Rt (min)
310		445	1.22
311		573	1.72

312		426	1.20
313		505	1.46
314		446	1.44

Preparation 10

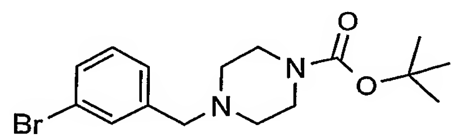
The derivatives of general structure **45** were prepared as depicted in Scheme 10. Mono-alkylation of the BOC-protected piperazine **42** with the benzyl bromide derivative **41**, followed by boration of the resulting bromide with trimethyl borate under strong basic conditions gave the corresponding boronic acid **43**. Further palladium coupling of **43** with 3-bromobenzonitrile, followed by reduction of the nitrile moiety produced compound **44**. In turn, compound **44** could be coupled with the appropriate carboxylic acids R_1CO_2H and deprotected to furnish the products **45**.

Scheme 10



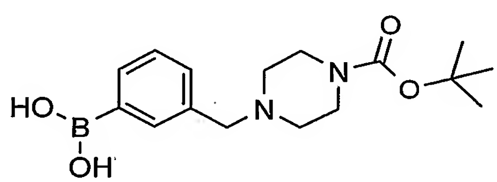
Conditions: a) TEA, CH_3CN, reflux, 16 h; b) n-BuLi, $B(OMe)_3$, THF, -70 °C; c) $Pd(PH_3)_4$, K_2CO_3, dioxan/water, mw, 150 °C, 15 min.; d) BH_3, THF, reflux, 1h; e) R_1CO_2H, PyBOP or HATU then TFA.

Intermediate 40: 1,1-dimethylethyl 4-[(3-bromophenyl)methyl]-1-piperazinecarboxylate



A solution of 3-bromobenzyl bromide (6 g, 24 mmol) and Boc piperazine (4.06 g, 12 mmol) in acetonitrile (30 mL) was treated with triethylamine (3.36 mL, 24 mmol). The resulting mixture was heated at reflux for 16 hours. After cooling to room temperature, the reaction mixture was treated with saturated sodium bicarbonate solution (20 mL), then extracted with ethyl acetate (2 x 30 mL). The organic phases were combined, dried with $MgSO_4$ and concentrated under vacuum. The residue was purified by chromatography on silica (100 g) eluting with ethyl acetate / cyclohexane to give the title compound (6.95g, 81.25%). LC/MS: m/z, 355, 357 (M+H), 2.40 min.

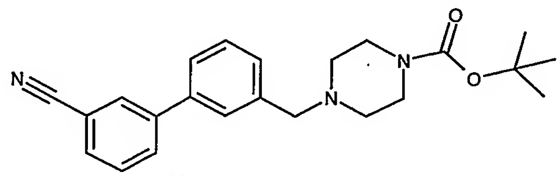
Intermediate 41: {3-[(4-{[(1,1-dimethylethyl)oxy]carbonyl}-1-piperazinyl)methyl]phenyl}boronic acid



To a solution of 1,1-dimethylethyl 4-[(3-bromophenyl)methyl]-1-piperazinecarboxylate (6.55 g, 18.5 mmol) in THF (20 mL) at -70°C was added dropwise n-butyl lithium (15.4 mL, 2.5 M solution in hexane, 38.5 mmol) over 10 minutes. After stirring for 30 mins at that temperature, the resulting orange solution was treated with trimethylborate (8.02 g, 77 mmol). The reaction mixture was then allowed to warm up to room temperature and quenched with saturated ammonium chloride (15 mL). The solvent was removed under vacuum and the residue was partitioned between ethyl acetate (20 mL) and water (20 mL). The aqueous phase was separated and further extracted with ethyl acetate (20 mL). The organic phases were combined, dried with $MgSO_4$ and evaporated under vacuum to give the title compound (5g, 84%) which was used directly for the preparation of 1,1-

dimethylethyl 4-[(3'-cyano-3-biphenylyl)methyl]-1-piperazinecarboxylate without further purification. LC/MS: m/z, 321 (M+H), 1.91 min.

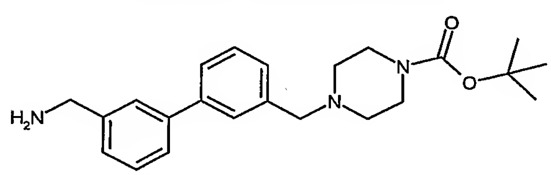
Intermediate 42: 1,1-dimethylethyl 4-[(3'-cyano-3-biphenylyl)methyl]-1-piperazinecarboxylate



A mixture of {3-[(4-{[(1,1-dimethylethyl)oxy]carbonyl}-1-piperazinyl)methyl]phenyl}boronic acid (1 g, 3.1 mmol), 3-bromobenzonitrile (0.56 g, 3.1 mmol), potassium carbonate (1.725 g, 12.5 mmol) and tetrakis triphenylphosphine palladium (180 mg) in dioxan/water (3:1, 4 mL) was sealed in a tube and heated at 150°C for 15 minutes in a microwave vessel. After cooling to room temperature, the reaction mixture was then diluted with water (25 mL) and extracted with ethyl acetate (2 x 25 mL). The combined organic phases were dried with $MgSO_4$ and concentrated under vacuum. The resulting crude residue was further purified by flash column chromatography on silica (100 g) to give the title compound (0.9 g, 76%) (purity ca 75%). LC/MS: m/z, 378 (M+H), 2.57 min.

Intermediate 43

1,1-dimethylethyl 4-{[3'-(aminomethyl)-3-biphenylyl]methyl}-1-piperazinecarboxylate



A solution of 1,1-dimethylethyl 4-[(3'-cyano-3-biphenylyl)methyl]-1-piperazinecarboxylate (4.5 g, 11.9 mmol) in THF (30 mL) was treated with borane in THF (47.7 mL, 1 M in THF, 47.7 mmol) and the resulting mixture was heated at reflux for 1 hour. After cooling to room temperature, the reaction mixture was quenched with saturated ammonium chloride solution (20 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organics were dried ($MgSO_4$), concentrated under vacuum to give a residue which was purified by flash

chromatography on silica (100 g) to yield the title compound (1.1g, 24.2%). LC/MS: m/z, 382 (M+H), 1.86 min.

Example 315: 3-(aminosulfonyl)-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide

A mixture of PyBOP (0.08 mmol in 200 mL of DMF), {[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}amine (44 mmol in 200 mL of DMF) and DIPEA (30 mL) were added to 3-(aminosulfonyl)benzoic acid (70 mmol). The resulting mixture was stirred for 16 hours at room temperature, then the solvent was removed under vacuum. The residue was dissolved in methanol and purified by loading onto a SPE cartridge (SCX, 500 mg), washing with MeOH, and eluting with a 2M solution of NH_3 in MeOH. The NH_3 fraction was collected and evaporated under vacuum to give a gum which was dissolved in 1:1 $CHCl_3$ / TFA (0.5 mL). After stirring for 2 hours, the solvent was removed under vacuum and the residue was dissolved in MeOH. The free base of the compound was obtained by loading the solution onto a SPE cartridge (SCX, 500 mg), washing with MeOH, and eluting with 2M NH_3/MeOH. The ammonia fraction was collected and the solvent was removed under vacuum to give the title compound (14.3 mg, 70%). LC/MS: m/z, 465 (M+H), 2.29 min.

The compounds listed in Table 23 were prepared proceeding in a similar manner to Example **315,** but replacing 3-(aminosulfonyl)benzoic acid with the appropriate acids.

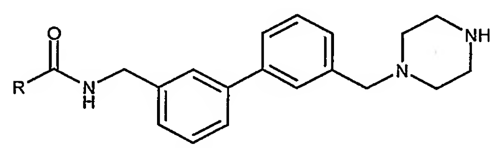
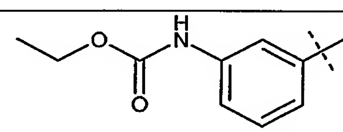
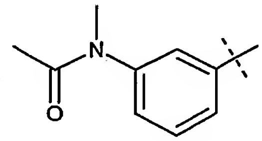
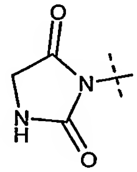
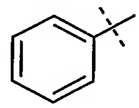
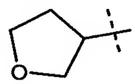
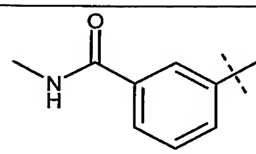
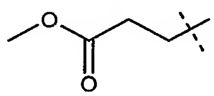
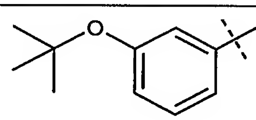
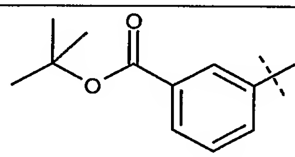
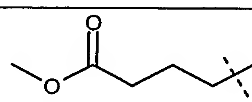
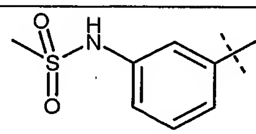
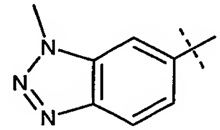
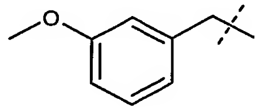
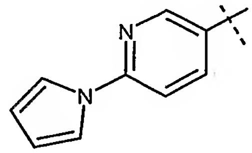
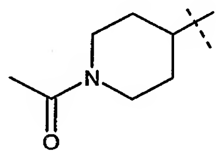
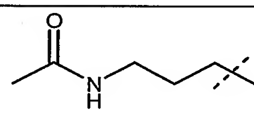
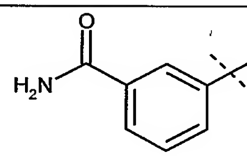
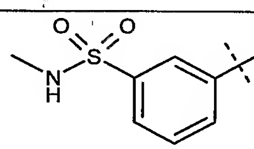
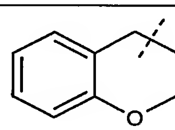
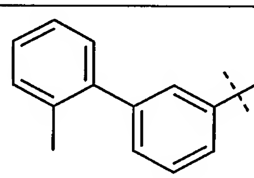
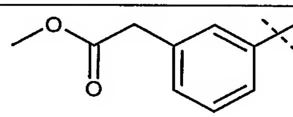
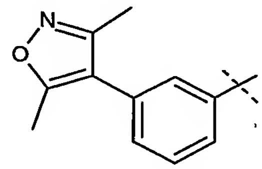
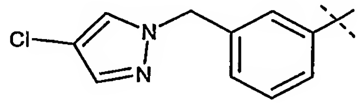
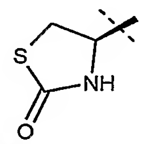
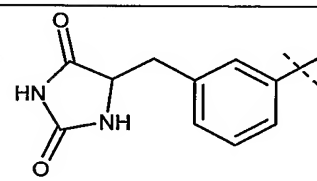
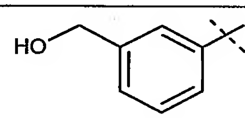
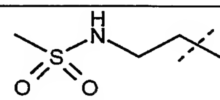
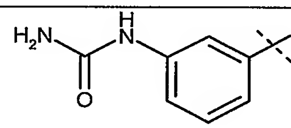
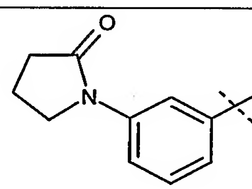


Table 23

Example	R	MS [MH]+	Rt
316		473	2.51

317		457	2.3
318		422	2.01
319		386	2.4
320		380	2.09
321		443	2.26
322		396	2.19
323		458	2.33
324		486	2.38
325		410	2.2
326		479	2.37

327		441	2.34
328		430	2.41
329		452	2.64
330		435	2.08
331		409	2.01
332		429	2.17
333		479	2.31
334		430	2.37
335		476	2.81
336		458	2.37

337		481	2.53
338		500	2.54
339		411	2.07
340		498	2.21
341		416	2.2
342		431	2.03
343		444	2.2
344		469	2.31

Example 345: 2-(4-oxo-4,5-dihydro-1,2,5-oxadiazol-3-yl)-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}acetamide trifluoroacetate

To a solution of (4-oxo-4,5-dihydro-1,2,5-oxadiazol-3-yl)acetic acid (0.1 mmol) in DMF (200 mL) was added a solution of HATU (0.1 mmol) in DMF (100 mL) followed by DIPEA (50 mL). After stirring for 10 minutes at room temperature, the mixture was treated with a solution of {[3'-(1-piperazinylmethyl)-3-

biphenylyl]methyl}amine (0.075 mmol) in DMF (200 mL). After stirring for 3 days, the solvent was removed under vacuum. The residue was dissolved in methanol and purified by loading onto a SPE cartridge (SCX, 500 mg), washing with MeOH (5 mL), and eluting with a 2M solution of NH_3 in MeOH (5 mL). The solvent was removed under vacuum and the resulting gum was dissolved in 1:1 $CHCl_3$ / TFA (0.5 mL). After stirring for 2 hours, the solvent was removed under vacuum to give a crude residue which was further purified by MDAP to afford the title compound as a TFA salt (3.8 mg, 10%). LC/MS: m/z, 408 (M+H), 2.18 min.

The compounds listed in Table 24 were prepared proceeding in a similar manner to Example **345**, but replacing (4-oxo-4,5-dihydro-1,2,5-oxadiazol-3-yl)acetic acid with the appropriate acids.

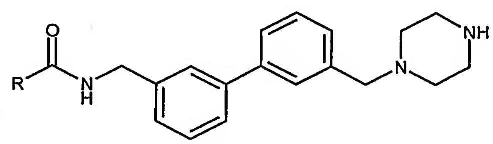
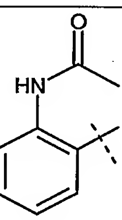
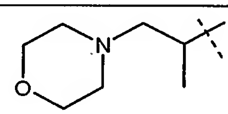
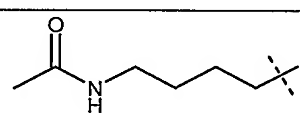


Table 24

Example	R	MS [MH] +	Rt
346		443	2.33
347		437	1.86
348		437	2.1

Example 349: N-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-2-(1H-1,2,3-triazol-1-yl)acetamide

A mixture of PyBOP (0.08 mmol in 200 mL of DMF), {[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}amine (44 mmol in 200 mL of DMF) and DIPEA (30 mL) were added to 1H-1,2,3-triazol-1-yl acetic acid (0.07 mmol). The resulting mixture was stirred for 16 hours at room temperature, the solvent was then removed under vacuum. The residue was re-dissolved in methanol and purified by loading onto a SPE cartridge (SCX, 500 mg), washing with MeOH (5 mL), and eluting with a 2M solution of NH_3 in MeOH (5 mL). The NH_3 fraction was collected and evaporated under vacuum to give a gum which was re-dissolved in 1:1 $CHCl_3$ / TFA (0.5 mL). After stirring for 2 hours, the solvent was removed under vacuum and the residue was purified by MDAP to give the desired compound as a TFA salt. The free base of the compound was obtained by loading the salt onto a SPE cartridge (SCX, 500 mg), washing with MeOH, and eluting with 2M NH_3/MeOH. The ammonia fraction was collected and the solvent was removed under vacuum to give the title compound (11.1 mg, 65%). LC/MS: m/z, 391 (M+H), 2.04 min.

The compounds listed in Table 25 were prepared proceeding in a similar manner to Example **349**, but replacing 1H-1,2,3-triazol-1-yl acetic acid with the appropriate acids.

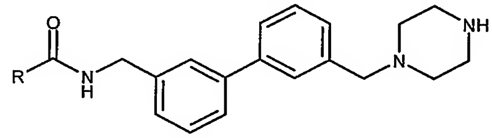
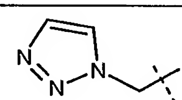
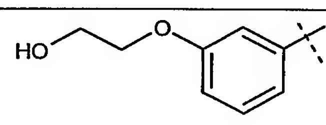
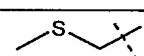
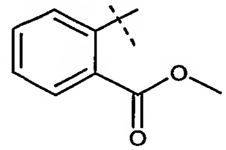
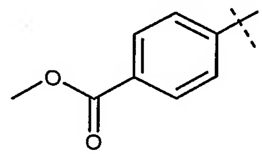
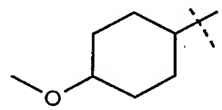
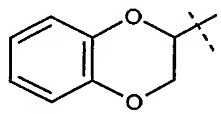
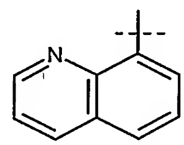
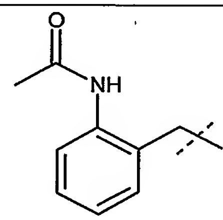
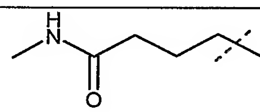


Table 25

Example	R	MS [MH]+	Rt
350		391	2.04
351		446	2.25
352		370	2.15

353		444	2.43
354		444	2.39
355		422	2.21
356		444	2.42
357		437	2.5
358		457	2.21
359		409	2.04

Abbreviations

BOC	tert-butyloxycarbonyl
DCM	Dichlromethane
DIC	1,3-Dissopropylcarbodiimide
DIPEA	Diisopropylethylamine
DMAP	Dimethylaminopyridine
DME	Dimethoxyethane

DMF	Dimethylformamide
DMHB	2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde
DMSO	Dimethylsulfoxide
EDCI	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EDC	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ESI	Electrospray ionization
EI-MS	Electrospray ionization-Mass spectrometry
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HOAc	Acetic acid
HOBt	Hydroxybenzotriazole
HPLC	High pressure liquid chromatography
LC/MS	Liquid chromatography/Mass spectrometry
MDAP	Mass directed automated preparative
mw	Microwave
NMP	1-Methyl-2-pyrrolidinone
NMR	Nuclear magnetic resonance
rt	Room temperature
SPE	Solid phase extraction
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

BIOLOGICAL EXAMPLES

The inhibitory effects of compounds at the M_3 mAChR of the present invention are determined by the following *in vitro* and *in vivo* assays:

Analysis of Inhibition of Receptor Activation by Calcium Mobilization:

1) 384-well FLIPR assay

A CHO (chinese hamster ovary) cell line stably expressing the human M3 muscarinic acetylcholine receptor is grown in DMEM plus 10% FBS, 2 mM Glutamine and 200 ug/ml G418. Cells are detached for maintenance and for plating in preparation for assays using either enzymatic or ion chelation methods. The day before the FLIPR (fluorometric imaging plate reader) assay, cells are detached, resuspended, counted, and plated to give 20,000 cells per 384 well in a 50 ul volume. The assay plates are black clear bottom plates, Becton Dickinson catalog number 35 3962. After overnight incubation of plated cells at 37 degrees C in a tissue culture incubator, the assay is run the next day. To run the assay, media are aspirated, and cells are washed with 1x assay buffer (145mM NaCl, 2.5mM KCl, 10mM glucose, 10mM HEPES, 1.2 mM $MgCl_2$, 2.5mM $CaCl_2$, 2.5mM probenecid (pH 7.4.) Cells are then incubated with 50ul of Fluo-3 dye (4uM in assay buffer) for 60 – 90 minutes at 37 degrees C. The calcium- sensitive dye allows cells to exhibit an increase in fluorescence upon response to ligand via release of calcium from intracellular calcium stores. Cells are washed with assay buffer, and then resuspended in 50ul assay buffer prior to use for experiments. Test compounds and antagonists are added in 25 ul volume, and plates are incubated at 37 degrees C for 5 -30 minutes. A second addition is then made to each well, this time with the agonist challenge, acetylcholine. It is added in 25 ul volume on the FLIPR instrument. Calcium responses are measured by changes in fluorescent units. To measure the activity of inhibitors / antagonists, acetylcholine ligand is added at an EC_{80} concentration, and the antagonist IC_{50} can then be determined using dose response dilution curves. The control antagonist used with M3 is atropine.

2) 96-well FLIPR assay

Stimulation of mAChRs expressed on CHO cells were analyzed by monitoring receptor-activated calcium mobilization as previously described. CHO cells stably expressing M_3 mAChRs were plated in 96 well black wall/clear bottom plates. After 18 to 24 hours, media was aspirated and replaced with 100 μl of load media (EMEM with Earl's salts, 0.1% RIA-grade BSA (Sigma, St. Louis MO), and 4 μM Fluo-3-acetoxymethyl ester fluorescent indicator dye (Fluo-3 AM, Molecular Probes, Eugene, OR) and incubated 1 hr at 37° C. The dye-containing media was then aspirated, replaced with fresh media (without Fluo-3 AM), and cells were incubated for 10 minutes at 37° C. Cells were then washed 3 times and incubated for 10

minutes at 37° C in 100 μl of assay buffer (0.1% gelatin (Sigma), 120 mM NaCl, 4.6 mM KCl, 1 mM $KH_2 PO_4$, 25 mM $NaH CO_3$, 1.0 mM $CaCl_2$, 1.1 mM $MgCl_2$, 11 mM glucose, 20mM HEPES (pH 7.4)). 50 μl of compound ($1x10^{-11}$ – $1x10^{-5}$ M final in the assay) was added and the plates were incubated for 10 min. at 37° C. Plates were then placed into a fluorescent light intensity plate reader (FLIPR, Molecular Probes) where the dye loaded cells were exposed to excitation light (488 nm) from a 6 watt argon laser. Cells were activated by adding 50 μl of acetylcholine (0.1-10 nM final), prepared in buffer containing 0.1% BSA, at a rate of 50 μl/sec. Calcium mobilization, monitored as change in cytosolic calcium concentration, was measured as change in 566 nm emission intensity. The change in emission intensity is directly related to cytosolic calcium levels . The emitted fluorescence from all 96 wells is measured simultaneously using a cooled CCD camera. Data points are collected every second. This data was then plotting and analyzed using GraphPad PRISM software.

Methacholine-induced bronchoconstriction

Airway responsiveness to methacholine was determined in awake, unrestrained BalbC mice (*n* = 6 each group). Barometric plethysmography was used to measure enhanced pause (Penh), a unitless measure that has been shown to correlate with the changes in airway resistance that occur during bronchial challenge with methacholine . Mice were pretreated with 50 μl of compound (0.003-10 μg/mouse) in 50 μl of vehicle (10% DMSO) intranasally, and were then placed in the plethysmography chamber. Once in the chamber, the mice were allowed to equilibrate for 10 min before taking a baseline Penh measurement for 5 minutes. Mice were then challenged with an aerosol of methacholine (10 mg/ml) for 2 minutes. Penh was recorded continuously for 7 min starting at the inception of the methacholine aerosol, and continuing for 5 minutes afterward. Data for each mouse were analyzed and plotted by using GraphPad PRISM software.

The present compounds are useful for treating a variety of indications, including but not limited to respiratory-tract disorders such as chronic obstructive lung disease, chronic bronchitis, asthma, chronic respiratory obstruction, pulmonary fibrosis, pulmonary emphysema, and allergic rhinitis.

FORMULATION-ADMINISTRATION

Accordingly, the present invention further provides a pharmaceutical formulation comprising a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative (e.g., salts and esters) thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

Hereinafter, the term "active ingredient" means a compound of formula (I), or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

Compounds of formula (I) will be administered via inhalation via the mouth or nose.

Dry powder compositions for topical delivery to the lung by inhalation may, for example, be presented in capsules and cartridges of for example gelatine, or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator. Powder blend formulations generally contain a powder mix for inhalation of the compound of the invention and a suitable powder base (carrier/diluent/excipient substance) such as mono-, di- or poly-saccharides (e.g., lactose or starch), organic or inorganic salts (e.g., calcium chloride, calcium phosphate or sodium chloride), polyalcohols (e.g., mannitol), or mixtures thereof, alternatively with one or more additional materials, such additives included in the blend formulation to improve chemical and/or physical stability or performance of the formulation, as discussed below, or mixtures thereof. Use of lactose is preferred. Each capsule or cartridge may generally contain between 20μg-10mg of the compound of formula (I) optionally in combination with another therapeutically active ingredient. Alternatively, the compound of the invention may be presented without excipients, or may be formed into particles comprising the compound, optionally other therapeutically active materials, and excipient materials, such as by co-precipitation or coating.

Suitably, the medicament dispenser is of a type selected from the group consisting of a reservoir dry powder inhaler (RDPI), a multi-dose dry powder inhaler (MDPI), and a metered dose inhaler (MDI).

By reservoir dry powder inhaler (RDPI) it is meant as an inhaler having a reservoir form pack suitable for comprising multiple (un-metered doses) of medicament in dry powder form and including means for metering medicament

dose from the reservoir to a delivery position. The metering means may for example comprise a metering cup or perforated plate , which is movable from a first position where the cup may be filled with medicament from the reservoir to a second position where the metered medicament dose is made available to the patient for inhalation.

By multi-dose dry powder inhaler (MDPI) is meant an inhaler suitable for dispensing medicament in dry powder form, wherein the medicament is comprised within a multi-dose pack containing (or otherwise carrying) multiple, define doses (or parts thereof) of medicament. In a preferred aspect, the carrier has a blister pack form, but it could also, for example, comprise a capsule-based pack form or a carrier onto which medicament has been applied by any suitable process including printing, painting and vacuum occlusion.

The formulation can be pre-metered (eg as in Diskus, see GB 2242134 or Diskhaler, see GB 2178965, 2129691 and 2169265) or metered in use (eg as in Turbuhaler, see EP 69715). An example of a unit-dose device is Rotahaler (see GB 2064336). The Diskus inhalation device comprises an elongate strip formed from a base sheet having a plurality of recesses spaced along its length and a lid sheet hermetically but peelably sealed thereto to define a plurality of containers, each container having therein an inhalable formulation containing a compound of formula (I) preferably combined with lactose. Preferably, the strip is sufficiently flexible to be wound into a roll. The lid sheet and base sheet will preferably have leading end portions which are not sealed to one another and at least one of the said leading end portions is constructed to be attached to a winding means. Also, preferably the hermetic seal between the base and lid sheets extends over their whole width. The lid sheet may preferably be peeled from the base sheet in a longitudinal direction from a first end of the said base sheet.

In one aspect, the multi-dose pack is a blister pack comprising multiple blisters for containment of medicament in dry powder form. The blisters are typically arranged in regular fashion for ease of release of medicament therefrom.

In one aspect, the multi-dose blister pack comprises plural blisters arranged in generally circular fashion on a disk-form blister pack. In another aspect, the multi-dose blister pack is elongate in form, for example comprising a strip or a tape.

Preferably, the multi-dose blister pack is defined between two members peelably secured to one another. US Patents Nos. 5,860,419, 5,873,360 and 5,590,645 describe medicament packs of this general type. In this aspect, the

device is usually provided with an opening station comprising peeling means for peeling the members apart to access each medicament dose. Suitably, the device is adapted for use where the peelable members are elongate sheets which define a plurality of medicament containers spaced along the length thereof, the device being provided with indexing means for indexing each container in turn. More preferably, the device is adapted for use where one of the sheets is a base sheet having a plurality of pockets therein, and the other of the sheets is a lid sheet, each pocket and the adjacent part of the lid sheet defining a respective one of the containers, the device comprising driving means for pulling the lid sheet and base sheet apart at the opening station.

By metered dose inhaler (MDI) it is meant a medicament dispenser suitable for dispensing medicament in aerosol form, wherein the medicament is comprised in an aerosol container suitable for containing a propellant-based aerosol medicament formulation. The aerosol container is typically provided with a metering valve, for example a slide valve, for release of the aerosol form medicament formulation to the patient. The aerosol container is generally designed to deliver a predetermined dose of medicament upon each actuation by means of the valve, which can be opened either by depressing the valve while the container is held stationary or by depressing the container while the valve is held stationary.

Spray compositions for topical delivery to the lung by inhalation may for example be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as a metered dose inhaler, with the use of a suitable liquefied propellant. Aerosol compositions suitable for inhalation can be either a suspension or a solution and generally contain the compound of formula (I) optionally in combination with another therapeutically active ingredient and a suitable propellant such as a fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof, particularly hydrofluoroalkanes, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetra-fluoroethane, especially 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or a mixture thereof. Carbon dioxide or other suitable gas may also be used as propellant. The aerosol composition may be excipient free or may optionally contain additional formulation excipients well known in the art such as surfactants eg oleic acid or lecithin and cosolvents eg ethanol. Pressurized formulations will generally be retained in a canister (eg an aluminium canister) closed with a valve (eg a metering valve) and fitted into an actuator provided with a mouthpiece.

Medicaments for administration by inhalation desirably have a controlled particle size. The optimum aerodynamic particle size for inhalation into the bronchial system for localized delivery to the lung is usually 1-10μm, preferably 2-5μm. The optimum aerodynamic particle size for inhalation into the alveolar region for achieving systemic delivery to the lung is approximately .5-3 μm, preferably 1-3 μm. Particles having an aerodynamic size above 20μm are generally too large when inhaled to reach the small airways. Average aerodynamic particle size of a formulation may measured by, for example cascade impaction. Average geometric particle size may be measured, for example by laser diffraction, optical means.

To achieve a desired particle size, the particles of the active ingredient as produced may be size reduced by conventional means eg by controlled crystallization, micronisation or nanomilling .The desired fraction may be separated out by air classification. Alternatively, particles of the desired size may be directly produced, for example by spray drying, controlling the spray drying parameters to generate particles of the desired size range. Preferably, the particles will be crystalline, although amorphous material may also be employed where desirable. When an excipient such as lactose is employed, generally, the particle size of the excipient will be much greater than the inhaled medicament within the present invention, such that the “coarse” carrier is non-respirable. When the excipient is lactose it will typically be present as milled lactose, wherein not more than 85% of lactose particles will have a MMD of 60-90μm and not less than 15% will have a MMD of less than 15μm. Additive materials in a dry powder blend in addition to the carrier may be either respirable, i.e., aerodynamically less than 10 microns, or non-respirable, i.e., aerodynamically greater than 10 microns.

Suitable additive materials which may be employed include amino acids, such as leucine; water soluble or water insoluble, natural or synthetic surfactants, such as lecithin (e.g., soya lecithin) and solid state fatty acids (e.g., lauric, palmitic, and stearic acids) and derivatives thereof (such as salts and esters); phosphatidylcholines; sugar esters. Additive materials may also include colorants, taste masking agents (e.g., saccharine), anti-static-agents, lubricants (see, for example, Published PCT Patent Appl. No. WO 87/905213, the teachings of which are incorporated by reference herein), chemical stabilizers, buffers, preservatives, absorption enhancers, and other materials known to those of ordinary skill.

Sustained release coating materials (e.g., stearic acid or polymers, e.g. polyvinyl pyrolidone, polylactic acid) may also be employed on active material or active material containing particles (see, for example, Patent Nos. US 3,634,582, GB 1,230,087, GB 1,381,872, the teachings of which are incorporated by reference herein).

Intranasal sprays may be formulated with aqueous or non-aqueous vehicles with the addition of agents such as thickening agents, buffer salts or acid or alkali to adjust the pH, isotonicity adjusting agents or anti-oxidants.

Solutions for inhalation by nebulation may be formulated with an aqueous vehicle with the addition of agents such as acid or alkali, buffer salts, isotonicity adjusting agents or antimicrobials. They may be sterilised by filtration or heating in an autoclave, or presented as a non-sterile product.

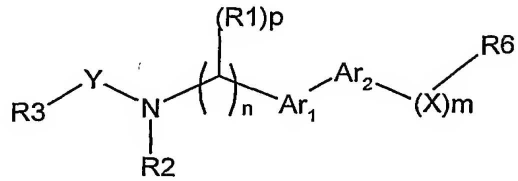
Preferred unit dosage formulations are those containing an effective dose, as herein before recited, or an appropriate fraction thereof, of the active ingredient.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is:

1. A compound of formula I as indicated below:



(I)

wherein

Ar1 and Ar2 are independently selected from the group consisting of optionally substituted phenyl and optionally substituted monocyclic heteroaryl;

R6 is NR_7R_8, or an optionally substituted saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more secondary or tertiary nitrogens, and optionally contain one or more O, or S;

X is C(R1)p, or C(O); wherein, when X is C(R1)p, m is an interger from 0 to 3; when X is C(O), m is 1;

p is an interger from 0 to 2;

n is an interger from 0 to 3;

Y is C(O), S(O)q, HNC(O), or OC(O); wherein, q is 1 or 2;

R1 and R2 are independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted heterocylic, optionally substituted heterocyclicalkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aryl alkyl, optionally substituted heteroaryl, and optionally substituted heteroaryl alkyl;

R3 is selected from the group consisting of optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkenyl, optionally substituted C_1-C_{10} alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted aryl alkyl, and optionally substituted heteroaryl alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of halogen, cyano, hydroxy, hydroxy substituted C_{1-10}alkyl, C_{1-10} alkoxy, $S(O)_{m'}$ C_{1-10} alkyl, C(O)R4, C(O)NR4R5; C(O)OH; $S(O)_2NR_4R_5$, $NHC(O)R_4$, $NHS(O)_2R_4$, C_{1-10} alkyl, alkenyl, halosubstituted C_{1-10} alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted

heteroaryl alkyl, wherein these aryl or heteroaryl moieties may be substituted one to two times by halogen, hydroxy, hydroxy substituted alkyl, C_{1-10} alkoxy, $S(O)_{m'}C_{1-10}$ alkyl, C_{1-10} alkyl, or halosubstituted C_{1-10} alkyl; and m' is 0, 1, or 2;

R_4 and R_5 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted aryl, optionally substituted aryl alkyl, optionally substituted heteroaryl, and optionally substituted heteroaryl alkyl; or R_4 and R_5 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O, and S;

R_7 and R_8 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, and optionally substituted heterocyclicalkyl; or R_7 and R_8 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O, N and S;

or a pharmaceutically acceptable salt thereof.

2. A. compound according to claim 1 selected from the group consisting of:

Ar1 and Ar2, are independently, selected from the group consisting of optionally substituted phenyl and optionally substituted monocyclic heteroaryl;

R6 is an optionally substituted saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more secondary or tertiary nitrogens;

X is C(R1)p, m is an interger from 0 to 3;

p is 2;

n is an interger from 1 to 3;

Y is C(O), or S(O)q; wherein, q is 1 or 2;

R1 is hydrogen

R2 is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted

heterocylic, optionally substituted heterocyclicalkyl, optionally substituted aryl, optionally substituted aryl alkyl, optionally substituted heteroaryl, and optionally substituted heteroaryl alkyl;

R3 is selected from the group consisting of optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkenyl, optionally substituted C_1-C_{10} alkyl, optionally substituted C_3-C_{10} cycloalkyl, and optionally substituted C_3-C_{10} cycloalkyl alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of halogen, cyano, hydroxy, hydroxy substituted C_{1-10}alkyl, C_{1-10} alkoxy, $S(O)_{m'}$ C_{1-10} alkyl, C(O)R4, C(O)NR_4R_5; C(O)OH; $S(O)_2NR_4R_5$, NHC(O)R_4, NHS$(O)_2R_4$, C_{1-10} alkyl, alkenyl, halosubstituted C_{1-10} alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroaryl alkyl, wherein these aryl or heteroaryl moieties may be substituted one to two times by halogen, hydroxy, hydroxy substituted alkyl, C_{1-10} alkoxy, $S(O)_{m'}C_{1-10}$ alkyl, C_{1-10} alkyl, or halosubstituted C_{1-10} alkyl; and m' is 0, 1, or 2;

R_4 and R_5 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted aryl, optionally substituted aryl alkyl, optionally substituted heteroaryl, and optionally substituted heteroaryl alkyl; or R_4 and R_5 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O, and S;

R_7 and R_8 are independently selected from the group consisting of hydrogen, optionally substituted C_{1-10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, and optionally substituted heterocyclicalkyl; or R_7 and R_8 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O, N and S;

or a pharmaceutically acceptable salt thereof.

3. A. compound according to claim 1 selected from the group consisting of:

Ar1 and Ar2, are independently, selected from the group consisting of optionally substituted phenyl and optionally substituted monocyclic heteroaryl;

R6 is an optionally substituted saturated or partially unsaturated 5-8 membered ring system in which one or more rings contain one or more secondary or tertiary nitrogens;

X is C(R1)p;

R1 is hydrogen

p is 2;

m is 1;

n is 1;

Y is C(O), or S(O)q;wherein, q is 1 or 2;

R2 is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted heterocylic, optionally substituted heterocyclicalkyl, optionally substituted aryl alkyl, and optionally substituted heteroaryl alkyl;

R3 is selected from the group consisting of optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkenyl, optionally substituted C_1-C_{10} alkyl, optionally substituted C_3-C_{10} cycloalkyl, and optionally substituted C_3-C_{10} cycloalkyl alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of halogen, cyano, hydroxy, hydroxy substituted C_{1-10}alkyl, C_{1-10} alkoxy, $S(O)_{m'}$ C_{1-10} alkyl, C(O)R4, C(O)NR_4R_5; C(O)OH; $S(O)_2NR_4R_5$, NHC(O)R_4, NHS$(O)_2R_4$, C_{1-10} alkyl, alkenyl, and halosubstituted C_{1-10} alkyl; wherein m' is 0, 1, or 2;

R_4 and R_5, are independently, selected from the group consisting of hydrogen, optionally substituted C_{1-10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted aryl, optionally substituted aryl alkyl, optionally substituted heteroaryl, and optionally substituted heteroaryl alkyl; or R_4 and R_5 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O, and S;

R_7 and R_8, are independently, selected from the group consisting of hydrogen, optionally substituted C_{1-10} alkyl, optionally substituted alkenyl,

optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, and optionally substituted heterocyclicalkyl; or R_7 and R_8 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O, N and S;

or a pharmaceutically acceptable salt thereof.

4. A. compound according to claim 1 selected from the group consisting of:

N-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-3-oxo-2,3-dihydro-1*H*-indene-5-carboxamide bis(trifluoroacetate);

N-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-3-propanoylbenzamide bis(trifluoroacetate);

3-acetyl-*N*-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

N-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-3-(2-oxopropyl)benzamide bis(trifluoroacetate);

3-(ethyloxy)-*N*-({6-fluoro-3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

3-acetyl-*N*-[(3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

3-cyano-*N*-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

3-acetyl-*N*-[(6-(methyloxy)-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

3-cyano-*N*-[(3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

N-({3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-6-fluoro-3-biphenylyl}methyl)-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

3-(ethyloxy)-*N*-({6-(methyloxy)-3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

N-[(3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

3-acetyl-*N*-({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

3-acetyl-*N*-[(3'-{[(3*R*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

N-{[6-fluoro-3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

methyl 3-{[({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)amino]carbonyl}benzoate bis(trifluoroacetate);

3-cyano-*N*-({3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-6-fluoro-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

3-cyano-*N*-({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

3-acetyl-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

3-cyano-*N*-[(6-(methyloxy)-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

3-(ethyloxy)-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

3-cyano-*N*-{[6-fluoro-4'-(methyloxy)-3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

N-({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

N-{[6-fluoro-4'-(methyloxy)-3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

3-(ethyloxy)-*N*-({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

3-acetyl-*N*-({3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

N-({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)-2,1,3-benzoxadiazole-5-carboxamide bis(trifluoroacetate);

N-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-2,1,3-benzoxadiazole-5-carboxamide bis(trifluoroacetate);

N-{[4',6-difluoro-3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

3-(methyloxy)-*N*-({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

3-cyano-*N*-{[4',6-difluoro-3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

3-cyano-*N*-{[6-(methyloxy)-3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

methyl 3-[({[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}amino)carbonyl]benzoate bis(trifluoroacetate);

3-(methylsulfonyl)-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

N-[3-(4-methyl-1-piperazinyl)propyl]-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}octanamide tetrakis(trifluoroacetate);

N-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

methyl 3-{[({3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-3-biphenylyl}methyl)amino]carbonyl}benzoate bis(trifluoroacetate);

3-cyano-*N*-{[3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-6-(methyloxy)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

N-({3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-3-biphenylyl}methyl)-3-(ethyloxy)benzamide bis(trifluoroacetate);

N-{[6-(methyloxy)-3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

N-({3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-3-biphenylyl}methyl)-2,1,3-benzoxadiazole-5-carboxamide bis(trifluoroacetate);

N-({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)-3-(methylsulfonyl)benzamide bis(trifluoroacetate);

3-cyano-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

N-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-3-(trifluoromethyl)benzamide bis(trifluoroacetate);

3-(methyloxy)-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

N-{[3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-6-(methyloxy)-3-biphenylyl]methyl}-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

N-[(3'-{[(3*R*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

3-cyano-*N*-[(3'-{[(3*R*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

N-({3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-3-biphenylyl}methyl)-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

N-({3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-3-biphenylyl}methyl)-3-(methylsulfonyl)benzamide bis(trifluoroacetate);

3-chloro-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

(*E*)-2-phenyl-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}ethenesulfonamide bis(trifluoroacetate);

3-cyano-*N*-({3'-[(1*R*,4*R*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

N-({3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-3-biphenylyl}methyl)-3-(methyloxy)benzamide bis(trifluoroacetate);

N-{[3'-(hexahydro-1*H*-1,4-diazepin-1-ylmethyl)-3-biphenylyl]methyl}-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

4-(methyloxy)-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzenesulfonamide bis(trifluoroacetate);

N-({3'-[(4-acetyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)-1,3-benzodioxole-5-carboxamide trifluoroacetate;

N-({3'-[(2,5-dimethyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

N-({3'-[(3-amino-1-pyrrolidinyl)methyl]-3-biphenylyl}methyl)-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

3-cyano-*N*-({3'-[(2,5-dimethyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

N-({3'-[(3-pyrrolidinylamino)methyl]-3-biphenylyl}methyl)-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

N-({3'-[(4-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

N-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-3-(phenylcarbonyl)benzamide;

3-(ethyloxy)-*N*-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide;

3-acetyl-*N*-[(4-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide;

3-(ethyloxy)-*N*-[(4-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide;

N-[(4-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-3-(phenylcarbonyl)benzamide;

N-[(4-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-1,3-benzodioxole-5-carboxamide;

3-(2-oxo-1-pyrrolidinyl)-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

methyl 2-[({[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}amino)carbonyl]benzoate;

3-[(4-chloro-1*H*-pyrazol-1-yl)methyl]-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

1-methyl-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-1*H*-1,2,3-benzotriazole-6-carboxamide;

3-[(2-hydroxyethyl)oxy]-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

3-[acetyl(methyl)amino]-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

3-[(3,4-dichlorophenyl)carbonyl]-*N*-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide;

3-ethyl-*N*-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide;

N-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide trifluoroacetate;

3-[(2,5-dioxo-4-imidazolidinyl)methyl]-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

methyl {3-[({[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}amino)carbonyl]phenyl}acetate;

3-(3-amino-4,5-dihydro-1*H*-pyrazol-1-yl)-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide trifluoroacetate;

2'-methyl-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-3-biphenylcarboxamide;

3-[(methylamino)sulfonyl]-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

N-methyl-*N'*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-1,3-benzenedicarboxamide;

3-(3,5-dimethyl-4-isoxazolyl)-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

3-[(methylsulfonyl)amino]-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

3-cyano-*N*-[(4-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide;

N-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-2-(3-pyridinyl)-1,3-thiazole-4-carboxamide;

3-acetyl-*N*-{[3-(6-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-2-pyridinyl)phenyl]methyl}benzamide trifluoroacetate;

N-{[3-(6-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-2-pyridinyl)phenyl]methyl}-3-(phenylcarbonyl)benzamide trifluoroacetate;

3-acetyl-*N*-{[3-(5-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-2-thienyl)phenyl]methyl}benzamide trifluoroacetate;

N-{[3-(6-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-2-pyridinyl)phenyl]methyl}-1,3-benzodioxole-5-carboxamide trifluoroacetate;

3-(hydroxymethyl)-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

3-(ethyloxy)-*N*-{[3-(6-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-2-pyridinyl)phenyl]methyl}benzamide trifluoroacetate;

N-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-1,3-benzenedicarboxamide;

N-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-8-quinolinecarboxamide;

3-(aminosulfonyl)-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

3-[(3,4-dichlorophenyl)carbonyl]-*N*-{[3-(6-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-2-pyridinyl)phenyl]methyl}benzamide trifluoroacetate;

N-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-6-(1*H*-pyrrol-1-yl)-3-pyridinecarboxamide; and

3-[(aminocarbonyl)amino]-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

or any other pharmaceutically acceptable salt, or non-salt form thereof.

5. A compound according to claim 1 selected from the group consisting of:

N-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-3-oxo-2,3-dihydro-1*H*-indene-5-carboxamide bis(trifluoroacetate);

N-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-3-propanoylbenzamide bis(trifluoroacetate);

3-acetyl-*N*-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

N-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-3-(2-oxopropyl)benzamide bis(trifluoroacetate);

3-(ethyloxy)-*N*-({6-fluoro-3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

3-acetyl-*N*-[(3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

3-cyano-*N*-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

3-acetyl-*N*-[(6-(methyloxy)-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

3-cyano-*N*-[(3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

N-({3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-6-fluoro-3-biphenylyl}methyl)-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

3-(ethyloxy)-*N*-({6-(methyloxy)-3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

N-[(3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

3-acetyl-*N*-({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

3-acetyl-*N*-[(3'-{[(3*R*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

N-{[6-fluoro-3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

methyl 3-{[({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)amino]carbonyl}benzoate bis(trifluoroacetate);

3-cyano-*N*-({3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-6-fluoro-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

3-cyano-*N*-({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

3-acetyl-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

3-cyano-*N*-[(6-(methyloxy)-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide bis(trifluoroacetate);

3-(ethyloxy)-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

3-cyano-*N*-{[6-fluoro-4'-(methyloxy)-3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

N-({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

N-{[6-fluoro-4'-(methyloxy)-3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

3-(ethyloxy)-*N*-({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

3-acetyl-*N*-({3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

N-({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)-2,1,3-benzoxadiazole-5-carboxamide bis(trifluoroacetate);

N-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-2,1,3-benzoxadiazole-5-carboxamide bis(trifluoroacetate);

N-{[4',6-difluoro-3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

3-(methyloxy)-*N*-({3'-[(3-methyl-1-piperazinyl)methyl]-3-biphenylyl}methyl)benzamide bis(trifluoroacetate);

3-cyano-*N*-{[4',6-difluoro-3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

3-cyano-*N*-{[6-(methyloxy)-3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

methyl 3-[({[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}amino)carbonyl]benzoate bis(trifluoroacetate);

3-(methylsulfonyl)-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

N-[3-(4-methyl-1-piperazinyl)propyl]-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}octanamide tetrakis(trifluoroacetate);

N-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-1,3-benzodioxole-5-carboxamide bis(trifluoroacetate);

methyl 3-{[({3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-3-biphenylyl}methyl)amino]carbonyl}benzoate bis(trifluoroacetate);

3-cyano-*N*-{[3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-6-(methyloxy)-3-biphenylyl]methyl}benzamide bis(trifluoroacetate);

N-({3'-[(1*S*,4*S*)-2,5-diazabicyclo[2.2.1]hept-2-ylmethyl]-3-biphenylyl}methyl)-3-(ethyloxy)benzamide bis(trifluoroacetate);

N-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-3-(phenylcarbonyl)benzamide;

3-(ethyloxy)-*N*-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide;

3-acetyl-*N*-[(4-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide;

3-(ethyloxy)-*N*-[(4-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide;

N-[(4-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-3-(phenylcarbonyl)benzamide;

N-[(4-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]-1,3-benzodioxole-5-carboxamide;

3-(2-oxo-1-pyrrolidinyl)-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

methyl 2-[({[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}amino)carbonyl]benzoate;

3-[(4-chloro-1*H*-pyrazol-1-yl)methyl]-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

1-methyl-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}-1*H*-1,2,3-benzotriazole-6-carboxamide;

3-[(2-hydroxyethyl)oxy]-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

3-[acetyl(methyl)amino]-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

3-[(3,4-dichlorophenyl)carbonyl]-*N*-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide;

3-ethyl-*N*-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide;

N-[(6-fluoro-3'-{[(3*S*)-3-methyl-1-piperazinyl]methyl}-3-biphenylyl)methyl]benzamide trifluoroacetate; and

3-[(2,5-dioxo-4-imidazolidinyl)methyl]-*N*-{[3'-(1-piperazinylmethyl)-3-biphenylyl]methyl}benzamide;

or any other pharmaceutically acceptable salt, or non-salt form thereof.

6. A Pharmaceutical composition for the treatment of muscarinic acetylcholine receptor mediated diseases comprising a compound according to claim 1 and a pharmaceutically acceptable carrier thereof.

7. A method of inhibiting the binding of acetylcholine to its receptors in a mammal in need thereof comprising administering a safe and effective amount of a compound according to claim 1.

8. A method of treating a muscarinic acetylcholine receptor mediated disease, wherein acetylcholine binds to said receptor, comprising administering a safe and effective amount of a compound according to claim 1.

9. A method according to claim 8 wherein the disease is selected from the group consisting of chronic obstructive lung disease, chronic bronchitis, asthma, chronic respiratory obstruction, pulmonary fibrosis, pulmonary emphysema and allergic rhinitis.

10. A method according to claim 9 wherein administration is via inhalation via the mouth or nose.

11. A method according to claim 10 wherein administration is via a medicament dispenser selected from a reservoir dry powder inhaler, a multi-dose dry powder inhaler or a metered dose inhaler.

12. A method according to claim 11 wherein the compound is administered to a human and has a duration of action of 12 hours or more.

13. A method according to claim 12 wherein the compound has a duration of action of 24 hours or more.

14. A method according to claim 13 wherein the compound has a duration of action of 36 hours or more.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/08302

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 31/495, 31/496, 31/407; C07D 295/155, 401/06, 487/04.
US CL : 514/253.01, 255.03, 412; 544/360, 393; 548/453.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/253.01, 255.03, 412; 544/360, 393; 548/453.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE STRUCTURE SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	US 2005/0131236 A1 (PETERS et al.) 16 June 2005 (16.06.2005) entire document.	1-14

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
10 July 2005 (10.07.2005)

Date of mailing of the international search report
29 JUL 2005

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US05/08302

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-3 and 6-14 (all in part)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Please See Continuation Sheet

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Continuation of Box II Reason 2:

Claims 1-3 and 6-14 relate to an extremely large number of permutations based on the scope of variables as generically set forth in the claims which are not all adequately supported in the description within the meaning of PCT Article 6. The claims have been searched based on the structure of species particularly claimed in claims 4 and 5.